Quarterly Progress Report

Technical and Financial

Hypoxia, Monitoring, and Mitigation System

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14. ABSTRACT
The HAMS program is progressing as expected with no technical issues to report. Partial FY2013 funding remains an issue, but additional funds are expected in November 2013 to continue the program. The concentrated effort on the literature search activity has been completed with moderate success and an FTP site has been created to share references and data among the team members. The baseline parametric algorithm to predict %O2 saturation and aircrew state has been converted to C and the initial conversion of the USN Consciousness Model has shown positive results and it appears that it will be possible to reduce the model to a size and complexity that will run on a modest microcontroller.

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1.0 Summary

This quarterly progress report discusses the technical and financial program status for the period of July 2013 through October 2013.

The Hypoxia Monitoring, Alert and Mitigation System (HAMS) program is progressing as expected with no technical issues to report. Partial FY2013 program funding remains an issue, but additional funds are expected in November 2013 to continue the effort without significant impact to the program.

The program consists of four baseline tasks and one optional task:

1. Preliminary Research and Documentation
2. Develop Parametric Predictive Models
3. Algorithm Development and Refinement
4. BETA Model Software Development/Definition
5. *Concept System Refinement (Option)*

Work has begun on Tasks 1, 2 and 3. Task 4 begins in January 2014 and the Task 5 option (not yet exercised) would begin in June 2014.

The concentrated effort on the literature search activity (Task 1) has been completed. A File Transfer Protocol (FTP) site has been created to share references and data among the team members and Office of Naval Research (ONR). The literature review to date has provided useful background information and general concepts, but no tangible validation data or definitive cognitive endpoints. The Reduced Oxygen Breathing Device (ROBD) data provided by NAVAIR will likely provide the best basis for establishing algorithm threshold limits for HAMS.

The baseline parametric hypoxia modeling effort (Task 2) to predict $\%O_2$ saturation, aircrew state, alveolar pressure of oxygen (PaO_2) and alveolar pressure of carbon dioxide ($PaCO_2$) originally programmed in MATLAB/SIMULINK has been converted over to the C programming language. This will allow the algorithm to eventually run on a micro-controller. Verification of the code conversion is underway currently.

The initial conversion of the United States Navy (USN) Consciousness Model (Task 3) has shown positive results and it appears that it will be possible to reduce the model to a size and complexity that will run on a modest microcontroller. The addition of a hypoxia component to the acceleration component of the model is underway.

We recommend that the program continue as scheduled assuming the remaining funding is obligated to the contract.

2.0 Introduction

Special Notice 13-SN-0003 outlined a research thrust entitled "Hypoxia Monitoring, Alert and Mitigation System" (HAMS) that was launched under the ONRBAA13-001. The desired features of the Hypoxia Monitoring, Alert, and Mitigation System were to predict/detect/warn warfighters of impending hypoxic events based on individual physiological, environmental, and cognitive monitoring. The stated goal was to provide optimal protection of military personnel and equipment through intelligent monitoring and adaptive modeling that accounted for individual differences in tolerance and provided timely notification/warning aids so personnel could take corrective action before compromise or loss. The team of Athena GTX (Athena) and Criterion Analysis Incorporated (CAI) collaborated, proposed and won an award under this effort.

This quarterly progress report discusses the technical and financial program status for the period of July 2013 through October 2013. It is intended to inform the Program Officer and Administrative Contracting Officer of the technical and financial progress of the HAMS program.

This algorithm development effort and the approach taken under this project is within the context that the algorithms developed will eventually need to run on a "fieldable" solution. Consequently the focus will be on algorithms that can run on micro-controller based platforms. As technology evolves from the laboratory into actual high altitude environments and is then coupled to stress of military operations the complexity of the issues this program addresses can be realized. Previous efforts to date have showed that attempting to reliably peer into the brain from the scalp surface through the skull with EEG and f-NIRS is neither comfortable nor feasible in a dynamic laboratory/simulator environment much less in an aircraft; and hence, in our experience, remains suspect for operational use. Perhaps this program will deliver such a solution; perhaps it is not feasible with today's technology. This by no means concludes that the technologies are not innovative or interesting or that they do not show promise, but the distance between a quiet, sedentary (perhaps anesthetized subject) and an aviator in flight or ground troops involves a tremendous leap of "technical courage". We believe the technology and processing abilities today will allow for a total change in focus from trying to integrate a comprehensive sensing solution into a flight or ground helmet to one where the needed solution is not actually near the head or helmet. This insight changes algorithm design. A small, lightweight, and comfortable monitoring system might eventually be designed to continuously measure multiple physiological parameters in an effort to track operator state and hypoxia, e.g., from the arm alone. Sensors which detect SpO2, pulse/pulse rate, ECG, and skin temperature will be researched and evaluated for integration feasibility with a tactile vibrator for alerting the user to the suspicion of growing hypoxia. Novel and non-traditional sensor locations and technologies will be investigated as they impact data and algorithm design issues, and advanced signal processing techniques applied, and compared in this program for extensive technology leveraging. However, all of this will be directly applicable to effective algorithm design. Each of the different measurements will be entered into a multi-parameter evolutionary prediction algorithm which outputs a numerical score that correlates to how prevalent any effects of hypoxia are to the user and to perhaps

suggest or anticipate the onset of hypoxia based on trend data. Depending on the hypoxia algorithm's output, a signal potentially will be sent wirelessly to an alarming device integrated into the sensing platform wirelessly, or located in a key area of the users life support to vibrate which will alert the user if preventative action needs to be taken. No sensing system is infallible so key iteration rate considerations will need to be established in the algorithm design earlier than thought necessary to maximize hypoxia code output characteristics and iteration rates needed.

3.0 Technical Progress

3.1 Task 1 – Preliminary Research and Documentation

The primary literature review effort has been completed. Research included internal online searches as well as utilizing research and data provided by Dr. Shender on behalf of the ONR. We have also created a secure online-site for collaboration of documents and data specifically for those involved with this program. We suspect that minor effort may continue throughout the project. As additional references and data are found they will be shared via the File Transfer Protocol (FTP) site.

Tangible validation data or definitive cognitive endpoints for the modeling and algorithm development efforts are still a need for the program and we have not been overly successful in finding this information in the literature to date. Interesting correlations for Autonomic Nervous System (ANS) system analysis and hypoxia predictions have been explored and could provide a path for prediction for the onset of hypoxia and are discussed in detail below. Summaries and abstracts of relevant literature search results are also included below. The literature has information available for directly measuring cerebral oxygen levels but to date these do not seem to be well suited to a product design for the HAMS applications. The abstracts of the remaining literature search results are included in Section 9.1.1 for completeness.

3.1.1 Significantly Relevant Literature Research Results

Stepanek J, Cocco D, Pradhan GN, Smith BE, Bartlett J, Studer M, Kuhn F, Cevette MJ. Early detection of hypoxia-induced cognitive impairment using the King-Devick test. Aviat Space Environ Med 2013; 84:1017 – 22.

The King-Devick test is cognitive screening test based on sequential rapid number reading aloud with performance based on a task performance time and errors. Subjects read a series of numbers from test cards, one demonstration and 3 test cards, lasting less than 2 minutes. The sum of the test cards times and the number of errors in reading the numbers constitutes the data. Twenty-five subjects were exposed for three minutes to hypoxic conditions via a gas mixture equivalent to 23,000 feet altitude whereupon they performed the test. Pre- and post-hypoxia exposure test controls were performed. Significant

differences were found during the hypoxia exposure compared to pre- and post-hypoxia controls which indicated that the test was sensitive to the stressor. Figure 1 below is from the paper (paper Figure 5) which shows the change in Oxygen saturation over the exposure averaged over all subjects. Oxygen saturation decreased from 98 ± 0.9% to 80 ± 7.8% after 3 minutes on hypoxic gas and continued to decline during the cognitive test 75.8 ± 8.3% at test completion. This study only indicates that the cognitive test is sensitive to hypoxia. Given the number of subjects and the standard deviations on oxygen saturation and test performance, some stratification of results based on oxygen saturation would have been useful to this project to help determine thresholds for hypoxia onset prediction.

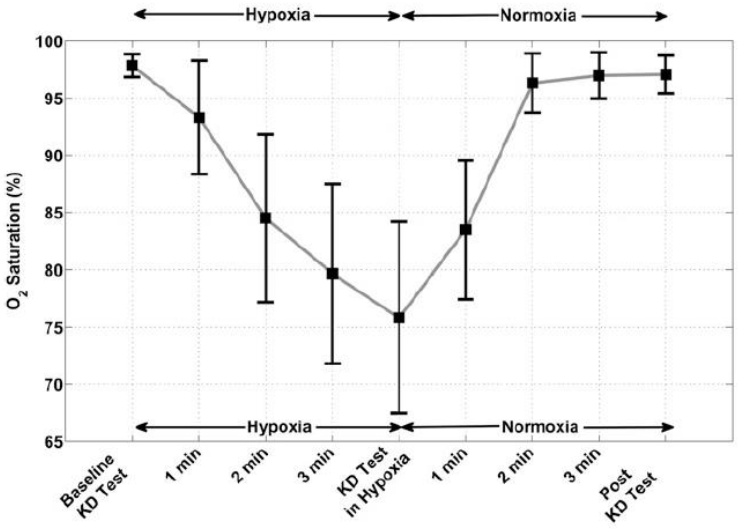


Figure 1 Oxygen Saturation for King-Devick Test Study

This recently published paper is like the majority of papers that put the subjects into a hypoxic state to measure performance decrement but don't correlate a measure like oxygen saturation to onset of cognitive decline.

Thresholds for hypoxia-induced psychomotor and cognitive decrement are needed to serve as warning indicators based on measured and predicted data. Given the beat-to-beat method in which oxygen saturation is measured via a pulse oximeter, a certain degree of "inexactness" exists. So it is unlikely that small differences in SaO2 will matter once a higher level threshold has been crossed. After an operationally relevant point further impairment thresholds would seem unnecessary. Fulco et al (1988) summarized the known data on the decrement in human performance in graphical form.

Fulco, C.S. & Cymerman, A. Human performance and acute hypoxia. In: Human Performance Physiology and Environmental Medicine at Terrestrial Extremes. (Chap 12), K.B. Pandolf, M.N. Sawka, and R.R. Gonzalez (Eds.) Benchmark Press, Indianapolis, IN: pp 467-495, 1988.

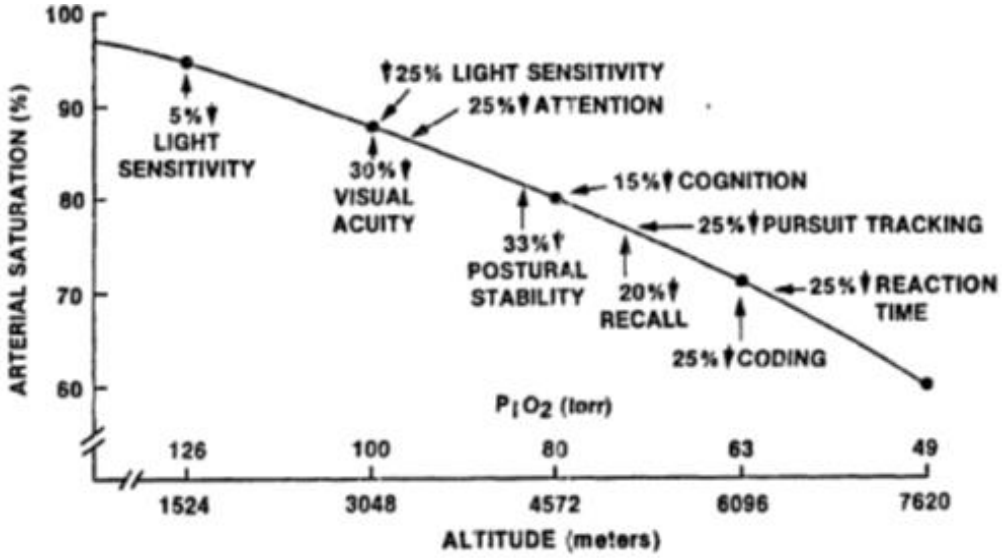


Figure 2 Human Performance Decrements by Oxygen Saturation and Altitude

Figure 2 (ref. Figure 6 in the publication from Fulco et al (1988)) indicates published decrements in human performance versus altitude and arterial saturation one of which may serve as a preliminary threshold for the measured pulse oximetry value. Loss of attention and visual acuity at arterial saturation of less than 90% but greater than 85% would be critical initial factors for the pilot or the ground soldier. This graph can be digitized to get more exact numbers where the original papers may be more difficult to obtain.

This paper also correlates to the discussion in Fundamentals of Aerospace Medicine (DeHart, 1985 page 98) where visual acuity is affected at 3048 meters and SpO2 is between 87% and 98% at altitudes between 0 and 3048 meters (10,000 feet). Above this altitude more serious detrimental conditions begin to emerge. The table below is from Table 5-13 in DeHart (1985).

Table 1. Stages of Hypoxia (from DeHart (1985))

Stage	Altitude Breathing Air (m)	%O2 Saturation
Indifferent	0 – 3048	98 – 87
Compensatory	3048 – 4572	87 – 80
Disturbance	4572 – 6072	80 – 65
Critical	6092 – 7010	65 – 60

3.1.2 Correlations between ANS and Hypoxia

Often the referenced literature focuses on one physiological measure to determine hypoxic state. However, the medical state of all individuals all the time usually mandates a multi-parameter assessment. Similarly one sensor cannot logically produce multiple measures without other sensors to produce "balance and reasonableness" to the output. Multiple physiological parameters that are used to quantify user conditions can be ascertained from SpO2, ECG, and temperature/humidity measurements. Heart rate, cardiac complexity, heart rate variability, pulse-wave transit time, shock index, modified shock index, and pulse integrity have been found to be good indictors of some health conditions, including hypoxia and hypovolemia, but a multi-parameter model need not differentiate between types of hypoxia (hypoxic, hypemic stagnant, histotoxic (DeHart, 1985)).

A multi-variable input and an adaptive scaling code will provide a single numerical value which corresponds to the urgency of state the subject as well as any trending of state apparent. Specifically, the diagnosis or reason for that state we express is not as important as the knowledge of the deterioration of that state as a combined score. Although the common baseline many feel is pulse oximetry we submit that the difficulty of obtaining a clean pulse oximetry signal in motion is extremely difficult. Similarly, obtaining a clean cerebral tissue measurement through the scalp is at best highly motion suspect. The effort cannot therefore overly focus on pulse oximetry and will attempt to derive measurement techniques centered at early ANS insult leading to hypoxia if uncorrected. But can we understand the role of the cardiovascular system and ANS relative to generation and management of hypoxia? The review completed to date has addressed this.

The time course changes in both cardiovascular and autonomic nervous system (ANS) function during acclimatization to altitude and hypoxia has been widely studied (e.g., Kawaguchi, et. al, 2003; Favret and Richalet, 2008; Barak, et. al, 2008; Hansen and Sander, 2002; Benoit, et.al., 1997, Iiyori, et. al., 2007/2008 (on line publications); Pellet, et. al., 1997, and Agostoni, et.al, 2000). The bulk of these studies suggest that the ANS insult defined as a notable change in activity is seen before the cardiovascular change is seen in many cases and many different trial designs. One might argue that this makes sense since the ANS drives the vascular response. Although obvious, this is a more difficult measure to take and much harder to interpret across any individual much less a population. But further, this suggests that looking for a physiological change in a vital sign recognized by the FDA in HAMS, may suggest that the event has already occurred and not that it is "going to" occur, i.e., that measure is not considered to be "anticipative" but "reactive to the event". In addition, the volatility of data seems to be demographically driven; i.e., the impact of age, sex and weight are clear. Finally, often the volatility of data is environmentally driven; i.e., the effect of cold and heat on the vascular response.

Consider the following. Barak, et.al. (2008) showed, for example, that the tolerance of a group of test subjects to hypoxia varies substantially among healthy subjects which supported earlier work that some individuals are simply ***better*** performers than others in the hypoxic environment (Stobdan, 2007). Similarly, the issue of exercise performance and ventilation control and the stimuli driving ventilation as

well as the mechanism of that control in hypoxia, drove a new research trend as much as ten years ago (Sheel, 2008, Longhurst, 2003). Longhurst's work neatly outlined the areas of compensation associated with a subject during progressive ascent to higher altitudes. Although we are not looking at progressive ascent, it proves a baseline consideration for the mechanisms expected to be seen in HAMS. Longhurst's work as well as Sheel's suggest that the HAMS must be reactively able to detect this compensation dynamically. As the human ascends, changes in cardiovascular parameters of heart rate (tachycardia), increased cardiac output and changes in flow distribution occur not only at minimal workloads but certainly at higher levels of stress and performance. In fact, Thompson, et al. (2004) showed that workload in acute hypoxia further exacerbates the issues of change locally since reduced gas tensions alters not only skeletal muscle performance, but heart rhythm and in other selected vascular beds such as the pulmonary arteries and lung tissues. This may lead to leakage, edema and dysfunction (Thompson, et. al, 2004). This in turn will impact gas exchange progressively, hence respiratory quotients, tissue oxygenation and carbon dioxide exhalation. Subsequently, subject acid base balance is progressively changed, progressive tissue toxicity may occur, and the overall result is that the subject's performance is expected to be spiraling downward. The changes or trends therefore become critical to track and measure as they may provide a better insight to prediction than the values alone.

From the perspective of the cardiovascular system, interactive response neural-hormonal mechanisms respond quickly during progressive hypoxia including local cardiac and direct vascular control. For example: studies in normally active subjects produced a three-fold increase in limb blood flow in hypoxia even in the presence of decreased ventricular stroke volumes (Kennedy, et. al, 2008). In normotensive environments, local responses are a direct result of autonomic outflow from the brainstem. Hypoxemia elicits the chemoreceptors, particularly those in the carotid bodies and the medulla, which can essentially oppose the changes driven by autonomic outflow (Guyton, 1976). Likely in the acute stages of hypoxia conflicting autonomic drives result in what one subject may manifest as normal ANS activity now progressively being disrupted. Heart Rate Variability (HRV) and cardiac complexity analysis of ECG RR-intervals provide measures of ANS tone (Barak, 2008). We know for example that higher workloads enhance the sympathetic and reduce the parasympathetic responses to the heart. Barak also showed over five years ago that higher workloads in hypoxemia hinder the typical response and the ratio as described above. Although the exact mechanisms of control and actions in higher workloads under the presence or absence of hypoxia are not fully delineated at this point in the literature since then (and likely not specifically agreed upon by researchers), we feel the near real time tracking of ANS integrity in the subject, while tracking subject movement or lack of movement via accelerometers, and heart rate complexity may provide an interesting insight as to the possibility of progressive hypoxia even in the simplest form without having a measure of blood or cerebral oxygen levels at all. To make this claim would also reap some disagreement from peers. However, what if this is true? Interestingly, this also suggests that when peripheral shutdown occurs due to increased sympathetic influences, and pulse oximetry begins to damp out, this ANS complexity may prove to be even more insightful. The linear stochastic HRV methods are more commonly known and understood and have been used in hypoxia assessment (Sugimura, et. al.

(2008)). One key thought from Wadhwa, et.al, (2008) however suggests that there is even an undefined stimulus not currently understood that is absent in normoxia subject states. If correct, this elicits the subject's ANS to increase oxygen delivery to the tissues during hypoxia. These stimuli may also be different in males versus females (Wadhwa, et. al., 2008) Hence, measuring hypoxia via blood oxygen levels alone or only at the cerebral level may not provide insight as to subjects impending hypoxic condition or state.

We conclude from the research done to date that measurement of autonomic activity, specifically using novel high speed DSP techniques to separate parasympathetic and sympathetic tone and looking for near real time changes in the activity as well as trends are clearly a step forward in assessing the progression of a clinically defined and progressive hypoxic condition well before the hypoxia is seen in any pulse oximetry system. Our literature support for this hypothesis is present but not overwhelming. However, as a projected product, the HAMS solution approaches would be foolish to abandon this option moving forward without thorough consideration and testing.

3.1.3 Relevant Aspects of USN Annotated Bibliography

- Increased age reduces the time before hypoxia appeared, therefore susceptibility to hypoxia increases with age
- Cerebral blood flow velocity was not a good indicator of mental stress during hypoxia
- Altitude dependent SaO2 values can be used to predict AMS susceptibility
- It took six days of acclimatization for balance to improve over sea-level base value.
- Hypoxia leads to a depressed cough reflex
- The effects of altitude may be specific to particular cognitive tasks; exercise during altitude results in decreased mental performance
- Hypoxic brain injury is reduce by administration of EPO
- Drugs such as alcohol and tobacco can worsen the effects of hypoxia on aviators
- Nicergoline offers protective properties against hypoxia-induced injury
- Low levels of taurine are associated with a higher susceptibility to hypoxia
- Hypobaric hypoxia causes a decrease in olfactory function
- HSP70 induced via GGA pretreatment significantly improved tolerance to acute hypoxia

3.1.4 Additional Relevant Literature Search Results

Abraini, J.H., Bouquet, C., Joulia, F., Nicolas, M., & Kriem, B. (1998). Cognitive performance during simulated climb of Mount Everest: implications for brain function and central adaptive processes under chronic hypoxic stress. *European Journal of Physiology, 463(4),* 553-559.

- Even though this is a slow ascent, it is controlled, not dynamic in impact and may serve as a corroborating study for establishing thresholds for risk of hypoxia and performance degradation.
- Put eight male climbers in a decompression chamber and gradually decompressed them to the altitude of Mount Everest over 31 days. Throughout the 31 days cognitive tests were

performed. They found that test subjects performed similar to control subjects up until 5,500 m to 6,500 m, where test subjects performance began to get worse compared to the control subjects.

- Limitations: Reasonably the limitations of this work are major. The eight subjects were all experienced climbers. The ascent was gradual rather than fast which would occur in an aircraft. Three subjects had transient strokes during the experiments.

Burtscher, Martin, et. al., (2012). Short-term exposure to hypoxia for work and leisure activities in health and disease: which level of hypoxia is safe? *Sleep Breath, 16,* 435-442.

- May serve as a corroborating study for establishing thresholds for risk of hypoxia and performance degradation.
- Looked to determine a safe altitude for people to be at for a "short" amount of time. Found that most high altitude conditions occur above 3000 m, and therefore that altitude is safe for most people. Exceptions include, women who are pregnant, people with diabetes or COPD, and children under 6 weeks.
- Limitations: does not ever specify "short" and "extended" periods of time and the exceptions are common sense. Also, Journal is not commonly seen. Peer review is not established.

Golja, P., Kacin, A., Tipton, M.J., Eiken, O., & Mekjavic, I.B. (Jun 2004). Hypoxia increases the cutaneous threshold for the sensation of cold. *European Journal of Applied Physiology, 92 (1-2),* 62-68.

- This may lead to looking at additional sensor modalities as part of HAMS to further refine and eliminate false positive/negative indications.
- Tested 13 male subjects ability to perceive a temperature change on their toe while breathing a hypoxic gas mixture. They found that a greater difference in temperature was required before a cold sensation was perceived while the test subjects were breathing either a hypobaric or a normobaric hypoxic mixture versus ambient air. There was no significant difference in temperature required to sense a warm sensation.
- Allows conclusions that environment impacts sensor performance and perception of the user.
- Other thoughts: If temperature perception is hindered, what about other touch sensations such as pressure, like the controls required to drive the air craft? (Depression in smell sensation during hypobaric hypoxia was shown in a different study).

King, Allen B., and Robinson, Summer M. (1972) Ventilation Response to Hypoxia and Acute Mountain Sickness. *Aerospace Medicine, 43*(4), 419-421.

- Information from this study may be used for a subject evaluation algorithm
- The study found that subjects who experienced the most severe symptoms of Acute Mountain Sickness, also shows a significant increase in minute ventilation during the first six hours of a 31 hours simulated decompression at 14,000 ft.
- Acute mountain sickness may also have an effect on cognitive ability, especially if symptoms are severe enough.

Martin, Russell L., et. al., (2000). Effect of Normobaric Hypoxia on Sound Localization. *Aviation, Space, and Environmental Medicine, 71*, 991-995.

- Study found that sound localization was not affected by hypoxia.
- May be contrary to other published papers
- Have found in numerous studies that some sensations are affected, and some are not, what causes this differences, and how can we use this to test or evaluate if someone is starting to become hypoxic.

Tauboll, Erik, et. al., (1997). Cerebral Artery Blood Velocity in Normal Subjects During Acute Decreases in Barometric Pressure. *Aviation, Space, and Environmental Medicine, 70,* 692-697.

- This may be used to more accurately model the effects of hypoxia
- Found that there is an increase in cerebral artery blood velocity due to a decrease in blood oxygen content rather than the decreased pressure, while studying patients in a hypobaric chamber with and without supplemental oxygen.
- Thoughts: Though a decrease in blood oxygen levels has a similar physiological response at sea level as when at low air pressure, would the introduction of supplemental oxygen cause the same physiological response at the same environments?

Yoneda, Ikuo, Tomoda, Masami, Tokumaru, Osamu, Sato, Tetsuo, and Watanabe, Yasuhiro. (2000). Time of Useful Consciousness Determination in Aircrew Members with Reference to Prior Altitude Chamber Experience and Age. *Aviation, Space, and Environmental Medicine, 71,* 72-76.

- This may be used to evaluate tolerance to hypoxia based on age
- This study compared the time of useful consciousness to the subject's age, and found that the younger subjects had a longer time of useful consciousness (TUC) and were more able to tolerate significantly lower SaO_2 levels.
- While decompressed to 25,000 ft. TUC of ages 39 and less was 237 seconds, and for those 40 and older was 202 seconds.

3.1.5 Data provided by ONR

In addition literature research, we also received data from ONR (Dr. Shender) which examined cognitive ability while utilizing a ROBD to simulate different altitudes. This data will be of tremendous value during the evaluation phase of this program. A sample of this data is show in Figure 3.

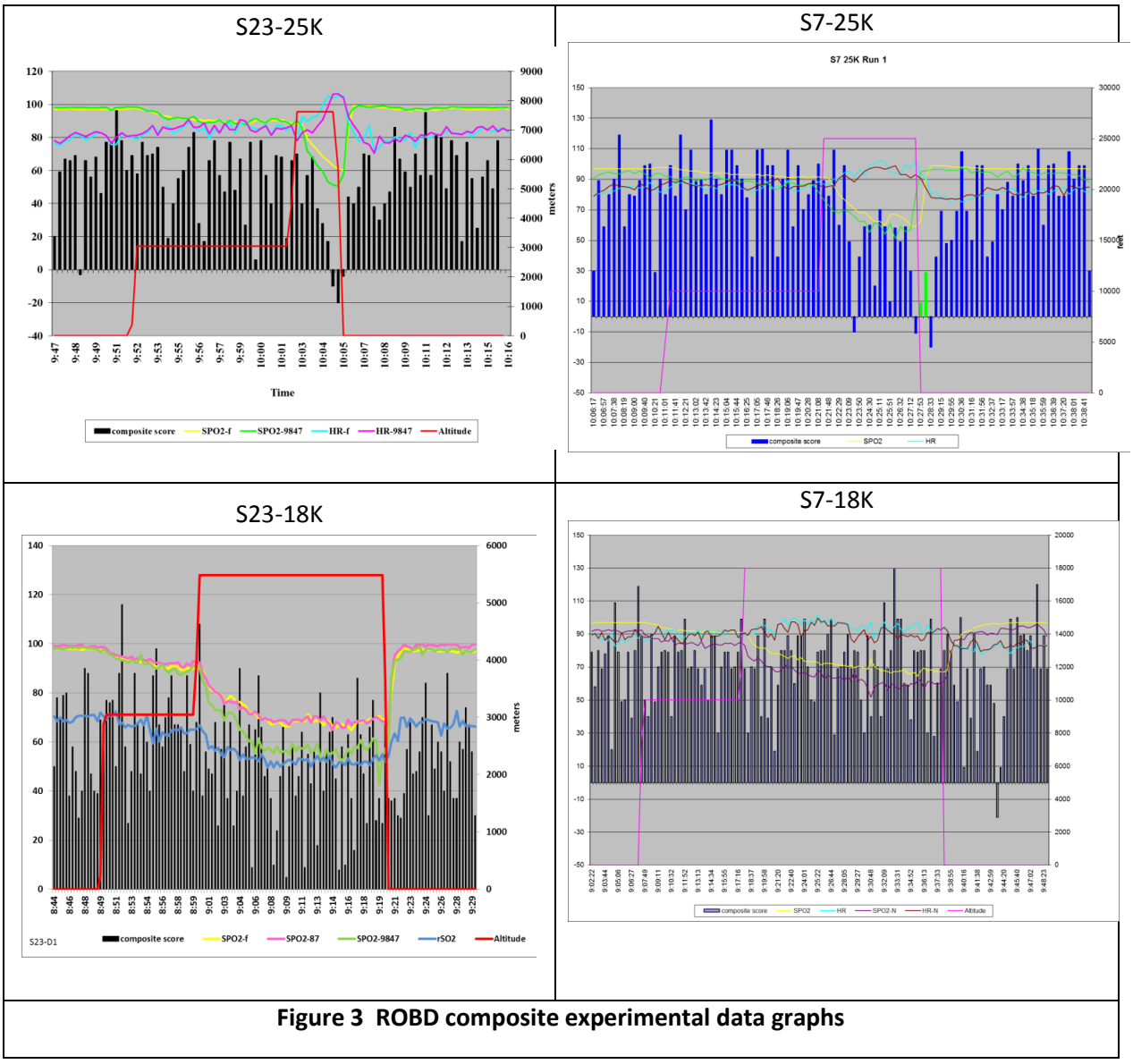


Figure 3 ROBD composite experimental data graphs

One key consideration of the ROBD data is the neuro-hormonal impacts of the device as compared to altitude chamber insult to the subject producing results. In turn the data produced will need special consideration as to the source. In reference, the data from lower negative body pressure chambers as opposed to hemorrhage has lent itself to some interesting debate with respect to the ANS triggers. In this case we will plan on examining the data and the device more closely as it applies to model development.

3.1.6 File Transfer Protocol Site

To facilitate collaborative research, the Athena GTX team has created a login protected FTP site where documents and data can be uploaded. New accounts for each user can be created as necessary and

additional documents and data may be shared using this tool. The procedure for obtaining a user account and brief instructions on how to use the site are provided in Section 9.1.2.

3.2 Task 2 – Develop Parametric Predictive Models

The baseline for this effort is the hypoxia modeling and prediction work done under the Tactical Aircrew Integrated Life Support System (TAILSS) program. We were successful in recovering the original MATLAB/SIMULINK files that were utilized in creating the final deliverables to the USN. The initial model, seen in Figure 4, predicts $\%O_2$ saturation, aircrew state, PaO_2 and $PaCO_2$ based on Altitude and the oxygen concentration of the breathing gas (See block diagram below). The code was implemented in SIMULINK for this project due to coordination with Carlton Technologies efforts for utilization of pulse dosing with ceramic oxygen generation in tactical aircraft. This implementation is not suitable for the HAMS implementation on an embedded system and therefore has been converted to C so that it is able to be embedded in a microcontroller/microprocessor.

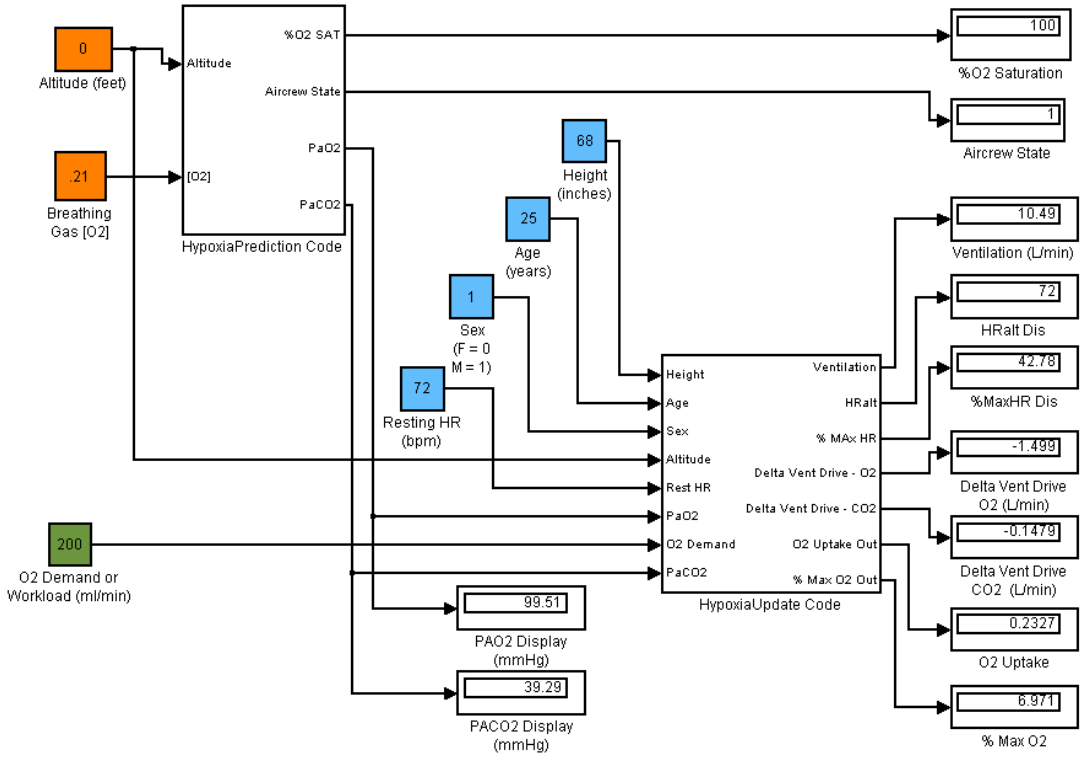


Figure 4. TAILSS Hypoxia Prediction Block Diagram (Initial Model in Simulink)

The below figure shows an example of the baseline hypoxia prediction algorithm output from the TAILSS program. The model produces an estimate of $\%SpO_2$ as a function of altitude (cabin) and breathing gas oxygen concentration. It also takes into account pH shifts based on a $PaCO_2$ estimate. The final output incorporates the following:

- Bounds for the SpO_2 (0 to 100%),
- a delay function and
- a transfer function

in order to produce a realistic response to changes in altitude. Although this can be used as a systems engineering design tool it is likely not biofidelic enough for HAMS. For the HAMS project our approach and goal is to further validate and more closely predict individual physiological responses.

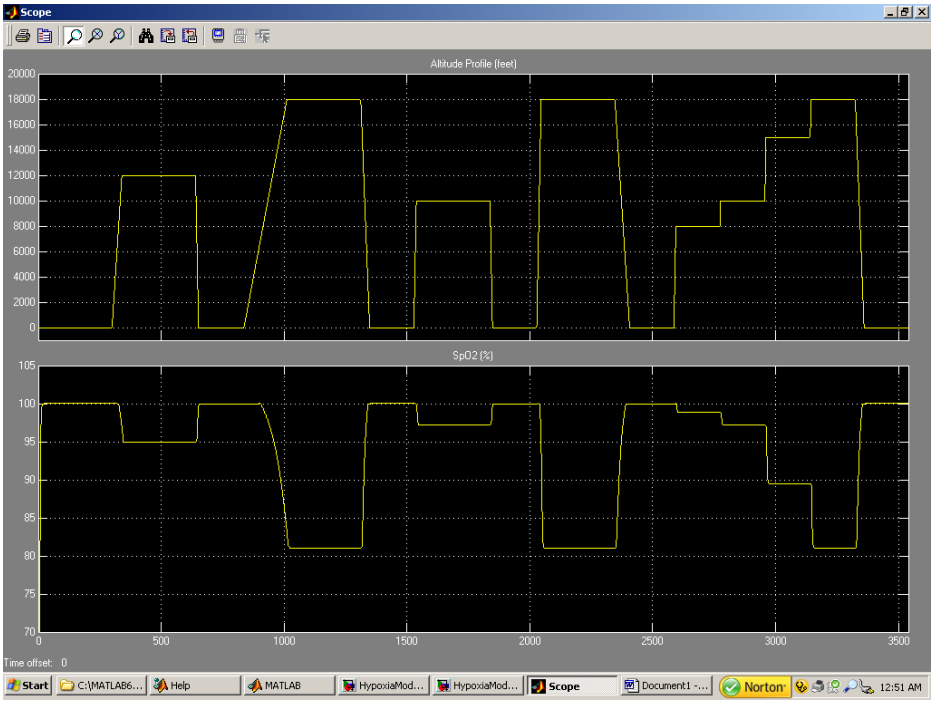


Figure 5. Example Output from the Baseline TAILSS Hypoxia Prediction Algorithm

A summary of the calculations is included below.

- Cabin pressure is derived by utilizing the 1976 COESA-extended US standard atmosphere model equations. Presently the constants for altitudes below 65,000 feet are included in the algorithm. This calculation can be eliminated in the future if a direct measurement of cabin pressure is available – leaving only a unit conversion to mmHg as applicable.
- PaCo2 is predicted as a functions of Cabin Pressure and then adjusted based on Altitude and [O2].
- Respiratory Exchange Ratio (RER) is also calculated based on Cabin Pressure.
- PaO2 is then predicted as a function of Cabin Pressure, [O2], RER and PaCO2.
- The PaCO2 prediction is then used to derive a pH adjustment factor to account for the shift in the O2 disassociation curve due to pH of the blood.

- The final %SpO2 is calculated as a function of PaO2 and the pH adjustment factor.
- The final time dependent %SpO2 output incorporates a time delay and transfer function.
- State is a simple function of SpO2 derived from Table 5-13 in DeHart (1985). (See Table below).

Table 2. Baseline Algorithm State and %O2 Saturation

State	%O2 Saturation	Stage
1	98 ≤ SpO2 ≤ 100	Normal
2	87 ≤ SpO2 < 98	Indifferent
3	80 ≤ SpO2 < 87	Compensatory
4	65 ≤ SpO2 < 80	Disturbance
5	0 ≤ SpO2 < 65	Critical

Based on the ROBD data provided, the time dependent functions of the algorithm need to be adjusted. The baseline model included a 4 second delay and about a 15 second response time to an altitude stressor. Review of the ROBD data and literature review articles suggests that the response time is minutes and not tens of seconds. The ROBD data also shows an increase in heart rate due to hypoxia stress. This was previously modeled and will be incorporated moving forward. Additional customization may be possible based on individual inputs such as Age, Height, Weight, Sex and Resting Heart Rate. These can be correlated to a prediction of workload and hence give a prediction of oxygen consumption or need which would be a negative influence on state if the subject is in a hypoxic environment.

Verification of the converted C code implementation is in the last stages with one bug remaining. This should be resolved early in the next reporting period. Once the C code is verified we will focus on the time dependent functions and the workload algorithm features to enhance the model for the HAMS specific application.

3.3 Task 3 – Algorithm Development and Refinement

3.3.1 Task 3a – Update the USN Consciousness Model Implementation

The USN Consciousness Model was written originally in Visual Basic 5.0 which is no longer supported and not easily converted to more modern languages since Microsoft evolved to the .net framework. The original code was stripped of Visual Basic 5.0 components and reconfigured for ExcelVBA under Excel 2010. Initial tests show comparability to the earlier model. This capability will allow rapid modification and testing to facilitate a smaller package.

A screen shot of the user interface page is shown in Figure 6.

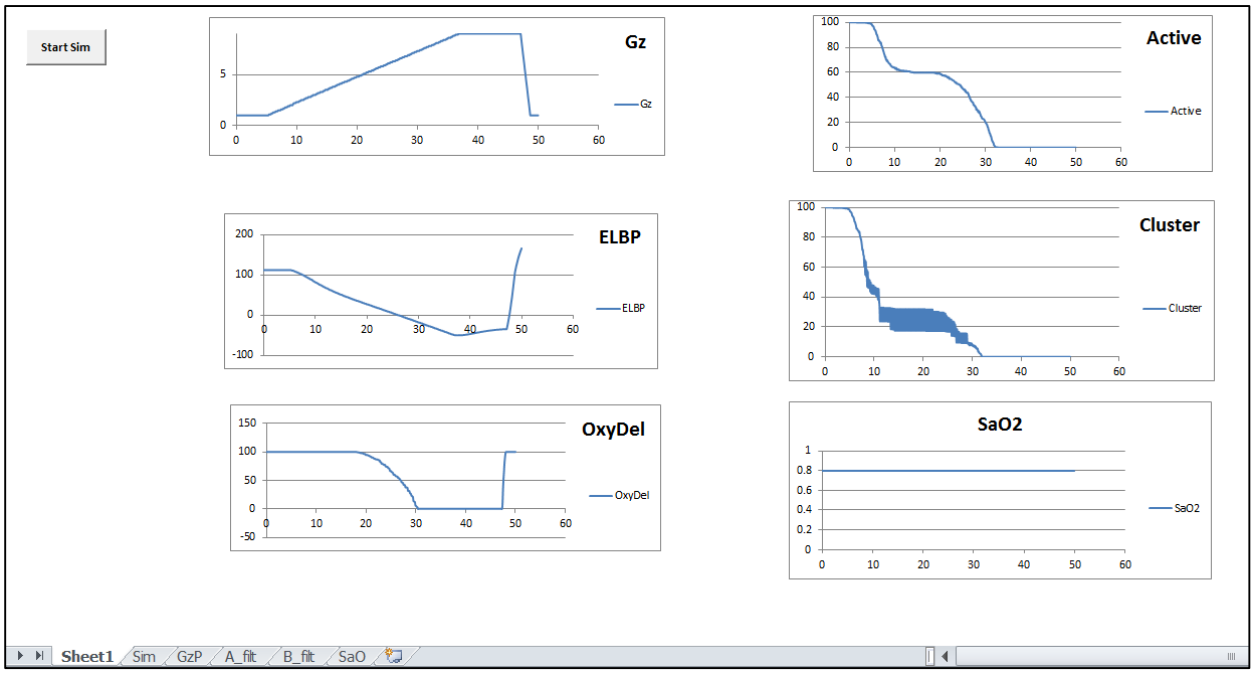


Figure 6 USN Consciousness Model in ExcelVBA

The simulation results are stored in the "Sim" tab, the input acceleration is stored in the "GzP" tab, the two oxygen utilization filters, A_flt and B_flt, are stored in their respective tabs , and the input SaO2 is stored in the "SaO" tab. The results have been compared to the original model running under Windows virtual XP mode either as the executable or under Visual Basic 5 where the same results are predicted, while not the exact same numbers calculated due to the intentional statistical variability imposed in the model. This new version, while not yet ready for dissemination pending further testing, will allow rapid modification of the code to shrink it to a smaller executable and storage memory footprint.

Since this effort is focused on developing algorithms that must run in an embedded environment (small, low power microcontroller/microprocessor), we explored the possibilities of reducing the original code and memory requirements. Some reduction in memory requirements are evident through cleaning up code and modification of computational methods. These has been further explored using the ExcelVBA model and are discussed below.

The USN Consciousness model is has a matrix-based formulation where the connectivity of the Reticular Activating System was mapped as grid of nodes as shown in Figure 7.

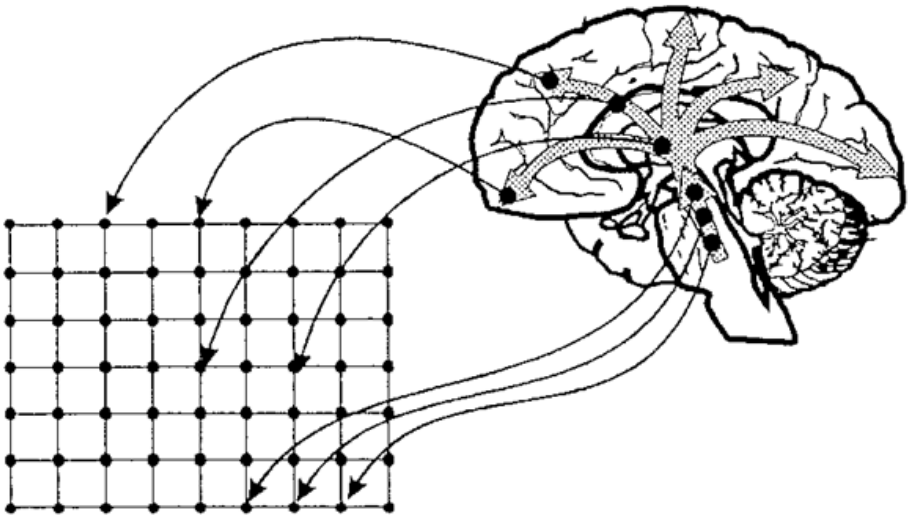


Figure 7 Matrix formulation of USN Consciousness Model

These nodes were active and connected when adequately perfused and oxygenated. These nodes were inactive and connection was lost when perfusion and oxygenation decreased. The model predicted reduction in "state" and unconsciousness when the connectivity in the grid from bottom to top was reduced or lost, respectively.

The grid of nodes formed the basis for 2 and 3 dimensional matrix formulation. A 20x20 element square matrix formed the basic grid and calculations were made based on matrix manipulation.

In considering the microcontroller storage requirements and where economies may be found only these matric variables will be considered at this point.

Table 3 Consciousness Model Current Variable Storage Requirements

Variable	Elements	Precision	Bytes	Total	Program Usage
z0(42, 42)	1764	Single	4	7056	Percolation calculation
OxySat(5, 42, 42)	8820	Single	4	35280	O2 utilization calculation
OxyDel(5, 42, 42)	8820	Single	4	35280	O2 delivery calculation
FilterNum(42, 42)	1764	Single	4	7056	Index into O2 utilization filter coefficient normal distribution
OxyOffThresh(42, 42)	1764	Single	4	7056	Randomized node on
OxyOnThresh(42, 42)	1764	Single	4	7056	Randomized node off
AOxy(100, 5)	500	Double	8	4000	O2 utilization filter coefficients
BOxy(100, 5)	500	Double	8	4000	O2 utilization filter coefficients
ACV(3)	3	Single	4	12	Eye level BP calc
BCV(3)	3	Single	4	12	Eye level BP calc
Gz(2000)	2000	Single	4	8000	Data-could be in a buffer
EyeBP(3)	3	Single	4	12	
Sa(2000)	2000	Single	4	8000	Data-could be in a buffer
GStress(3)	3	Single	4	12	
hScale(42, 42)	1764	Single	4	7056	Hydrostatic column distribution

Total of 129,888 bytes

Possible areas of reduction are the input data for Gz and SaO2 since these will be likely 2-byte values but computationally as read in as an array into a program may expand. The matrix sizes are all allocated as 42 x 42 but in the code the actual size of the node matrix is 20 x 20. Work recently completed in the Hammerhead™ program reduced the matrix sizes to minimize data throughput. If this was just a

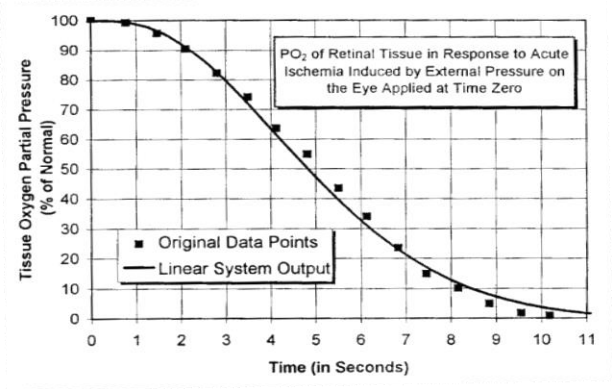
convenience left in while determining the optimum node matrix size, the size can henceforth be easily adjusted. The calculations for oxygen delivery and saturation (level), indicated as highlighted in yellow, have been identified as having the best chance for memory requirements reduction. The matrix format of these calculations relate to the node matrix and introduction of statistical variability but some of this may be calculated as needed and statistical process applied then. Understanding of the oxygen utilization filter calculation is essential before making any modifications. This is discussed in the next section.

Oxygen Utilization Filter

Examining the model code the oxygen utilization filter A and B coefficients are look-up tables which hold four coefficients for this calculation. These coefficients are "hard wired" into the code so that they must take up space of any program code which is at a premium for small, low power processors. The actual number values from the original software contain a significant number of significant digits. The B coefficients are quite small, on the order of 10^{-4}, and the A coefficients are more reasonable in terms of number representation. To be able to reduce or eliminate the memory overhead, one must understand what is being calculated.

Cammarota, in his original thesis, utilized the retinal oxygen depletion represented characteristically in

Figure 8 which he represented as the system response to a step function (step pressure to stop blood flow to the eye) in the H(s) equation indicated below.



$$H(s) = \frac{1}{(s + 6.667)(s + 0.4)(s + 0.4 \pm j0.4)}$$

Figure 8 Retinal oxygen utilization

This s-domain equation cannot be used to operate on data in the time domain. The H(s) system response was expanded in SciLab (version 5.4.1) to give a polynomial denominator and then converted into the z domain using the bilinear transformation using SciLab to derive the equation below:

$$H(z) = \frac{0.0000044 + 0.0000177z^{-1} + 0.0000265z^{-2} + 0.0000177z^{-3} + 0.0000044z^{-4}}{0.44345 - 2.27083z^{-1} + 4.20826z^{-2} - 3.38083z^{-3} + z^{-4}}$$

Examining the coefficients in the A and B filter matrices, those values correspond exactly in characteristic (sign) and magnitude (not the exact number but close) to the denominator for A and the numerator for B. The z domain equation directly becomes a difference equation whereby the time history data values can be operated on. The 3 dimensional matrices for OxySat and OxyDel are basically holding the result and intermediate values for the filter calculation. The essential flow of the program is that the eye level blood pressure is changed by the Gz(n) value which changes the oxygen delivery (the input) which the output (oxygen saturation) can be computed with the filter. Oxygen delivery will be the result of an offset SGN function based on eye level blood pressure and normal blood pressure. The representative blood pressures at the nodes are randomized based on values of the hScale matrix. The z0 matrix will be either set to 0 or 1 based on the threshold to turn on and off and then the percolation calculation through the matrix will occur resulting in a determination of connectivity. Some reduction in memory requirements may be possible by using the mean filter coefficients to calculate an oxygen saturation value and then applying statistical process to the result by node location. This modification would eliminate storing the filter coefficients in a matrix and also the filter number index matrix. The OxySat and OxyDel matrices may reduce to 20 x 20 and just hold the result at the node matrix size with no intermediate results needed. There is no indication that a time series average is being processed, just access to the filter coefficients.

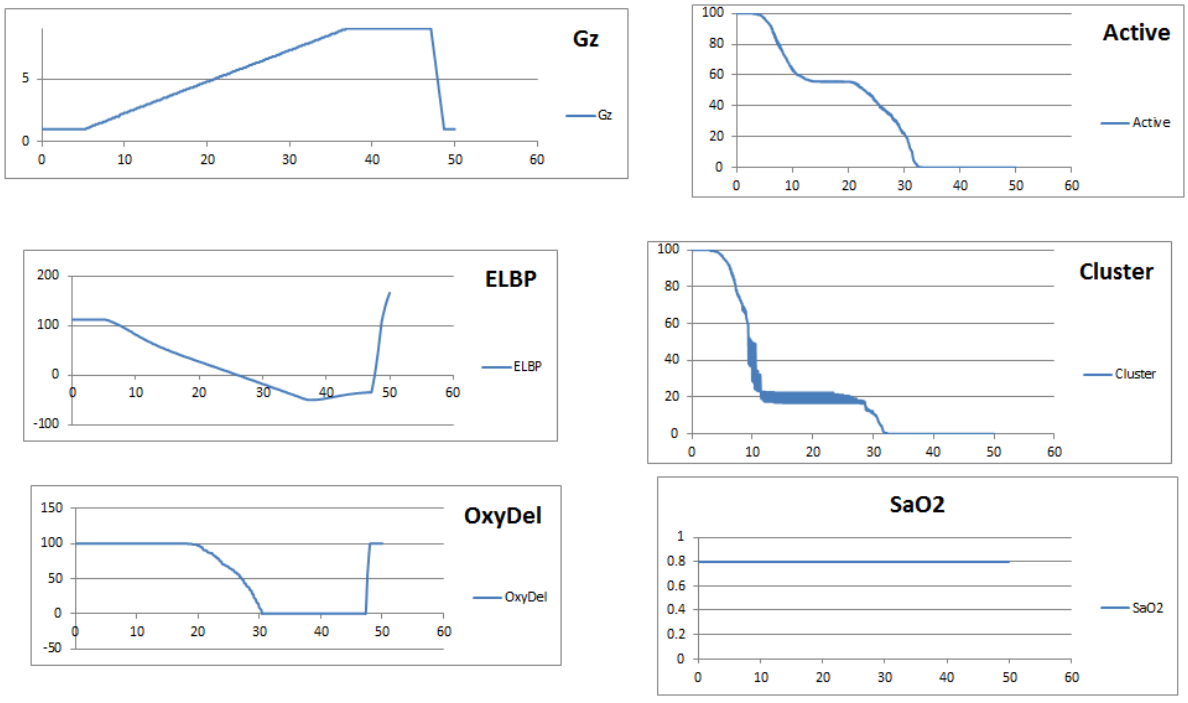
As discussed above the algorithm matrix formulations used are a 20x20 element square matrix and the original storage dimensions were changed based on that reduction as indicated in Table 4. Reducing the matrix sizes to the correct value resulted in a 77% reduction of space requirements for those matrices. The model formulation used oxygen utilization filter coefficients generated in a statistically varied way with respect to standard deviation and then selected the filter coefficient set through a table of statistically generated filter numbers. Eliminating the three matrices associated with the oxygen utilization filter resulted in close to a 15,000 byte reduction in storage requirements. Overall the storage requirements were reduced to a quarter of the original calculation to approximately 34,000 bytes as seen in Table 4.

Table 4 Consciousness Model Current Variable Storage Requirements

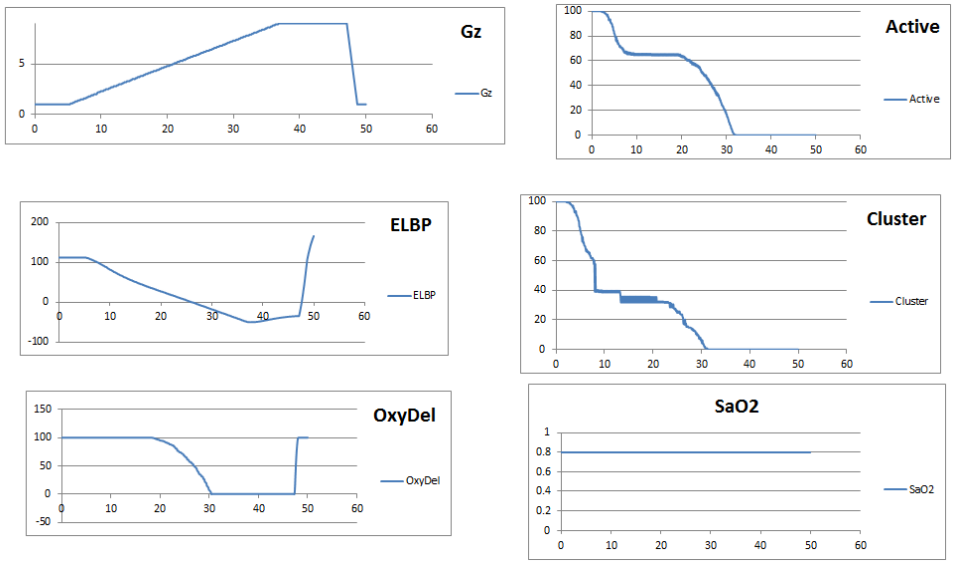
Variable	Elements	Precision	Bytes	Total Bytes	Variable	New Total Bytes	Reduction
z0(42, 42)	1764	Single	4	7056	z0(20, 20)	1600	77%
OxySat(5, 42, 42)	8820	Single	4	35280	OxySat(5, 20, 20)	8000	77%
OxyDel(5, 42, 42)	8820	Single	4	35280	OxyDel(5, 20, 20)	8000	77%
FilterNum(42, 42)	1764	Single	4	7056	**eliminated**	0	-
OxyOffThresh(42, 42)	1764	Single	4	7056	OxyOffThresh(20, 20)	7056	0%
OxyOnThresh(42, 42)	1764	Single	4	7056	OxyOnThresh(20, 20)	7056	0%
AOxy(100, 5)	500	Double	8	4000	**eliminated**	40	99%
BOxy(100, 5)	500	Double	8	4000	**eliminated**	40	99%
ACV(3)	3	Single	4	12	ACV(3)	-	-
BCV(3)	3	Single	4	12	BCV(3)	-	-
Gz(2000)	2000	Single	4	8000	Gz(2000)	Buffer	TBD
EyeBP(3)	3	Single	4	12	EyeBP(3)	-	-
Sa(2000)	2000	Single	4	8000	Sa(2000)	Buffer	TBD
GStress(3)	3	Single	4	12	GStress(3)	-	-
hScale(42, 42)	1764	Single	4	7056	hScale(20, 20)	1600	77%

Starting total of 129,888 bytes compared to current total of 33,392 (excluding data buffers)

A single oxygen utilization calculation was used for each node point and a comparison screenshot of results is shown in Figure 9.



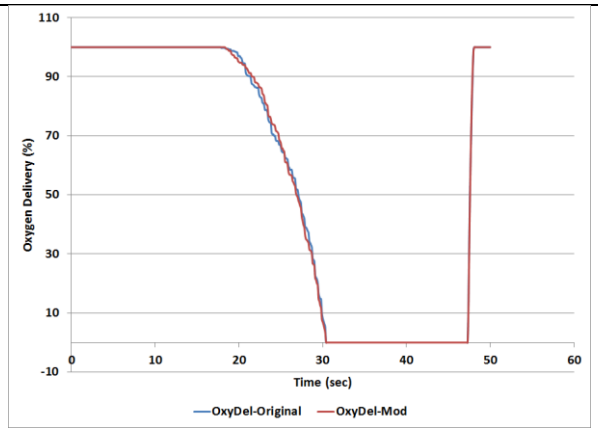
Original ExcelVBA Oxygen Utilization Filter



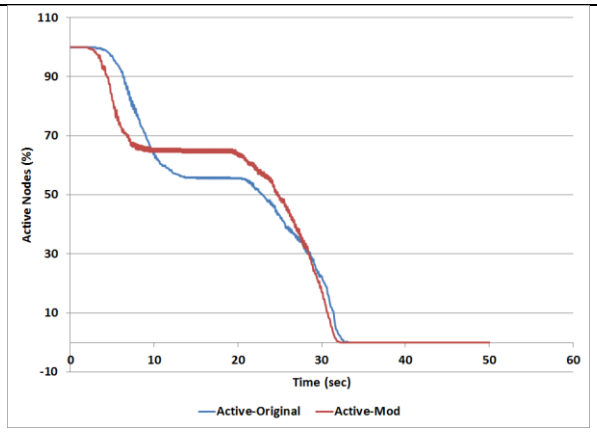
Modified ExcelVBA – Single Set of Oxygen Utilization Filter Coefficients

Figure 9 Comparison of Original and Modified VBA Algorithms

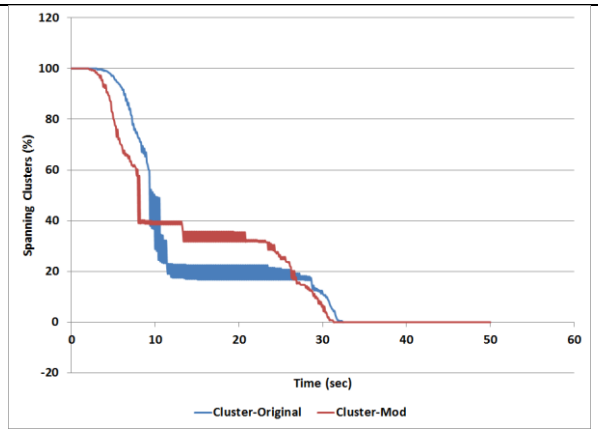
Comparison model results are shown in Figure 10.



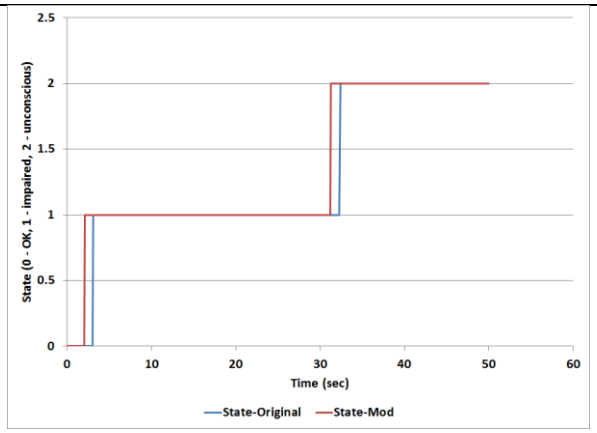
Oxygen Delivery



Active Nodes



Spanning Clusters



State

Figure 10 Comparison of Simulation Results from Algorithm Modification

Oxygen delivery should agree closely since no changes are made with that calculation. The percentage of active nodes and spanning clusters differ somewhat by transition timing and level but generically the changes occur at about the same time and to the same levels. The predicted states change at essentially the same times with the modified calculation changing slightly earlier than the original method.

3.3.2 Task 3b – Determine Model Deficiencies for Hypoxia

The HAMS consciousness model works on the basis of rapid cessation of perfusion causing tissue/cell level oxygen reduction without regard for longer time course metabolism having any influence. This approach

will not be sufficient for hypoxic hypoxia and a factor that reduces SaO2 based on metabolism and work rate is needed even when oxygen delivery is fine to fully encompass the scope of anticipated utilization.

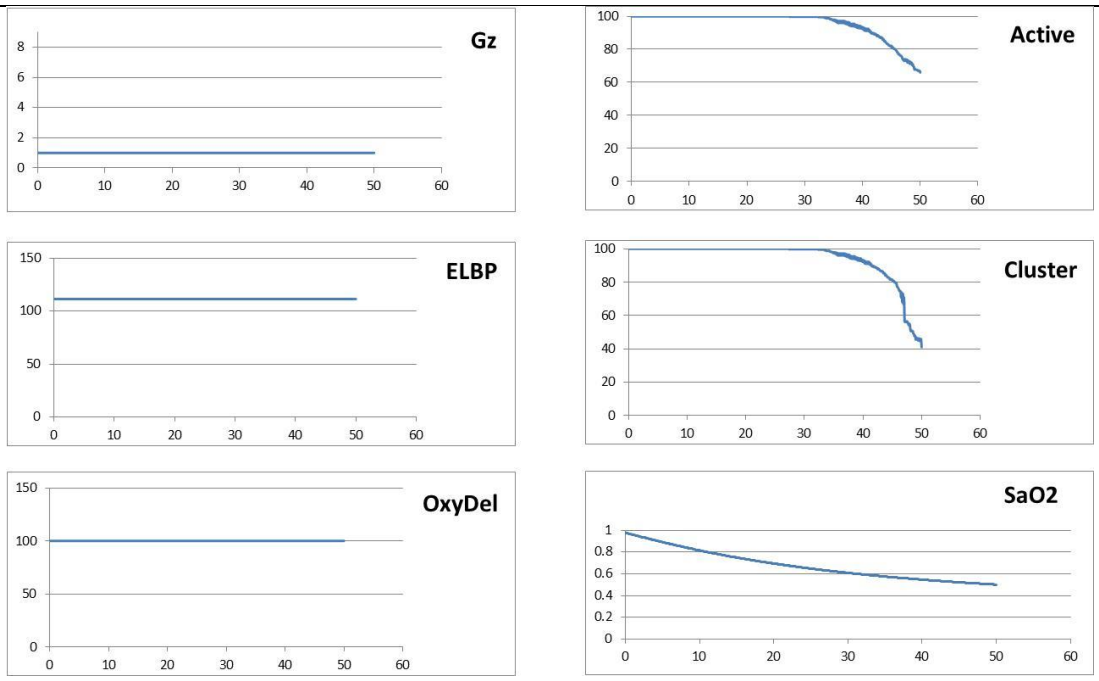
The desired relationship has not been found in the literature. At this point, we theorize that a series of runs with HumMod is needed to develop an oxygen utilization rate equation based on long time course hypoxia conditions alone to supplement the current oxygen consumption methodology. Initial work toward this end is discussed later in this section of the report. We will be exploring the validity of this approach as well as the potential for using alternate workload prediction algorithms used in previous Athena GTX projects such as the Hammerhead™ and DogBone™. This is particularly noteworthy for potential end users in ground operations and deploying to the ground in high altitude conditions.

The model mean node "off" threshold setting was varied and the effect examined with the SaO_2 time history from an immediate 40,000 ft. altitude exposure at normal gravity generated using HumMod (Version 1.6.1) and then acceleration response examined with an arbitrary 7G exposure to induce GLOC. An optimum mean "off" threshold of 0.8 was determined based on rapidity of predicting impairment and the altitude and acceleration exposures were combined for a simulation and the results are shown. Table 5 shows the summary prediction times while varying threshold level.

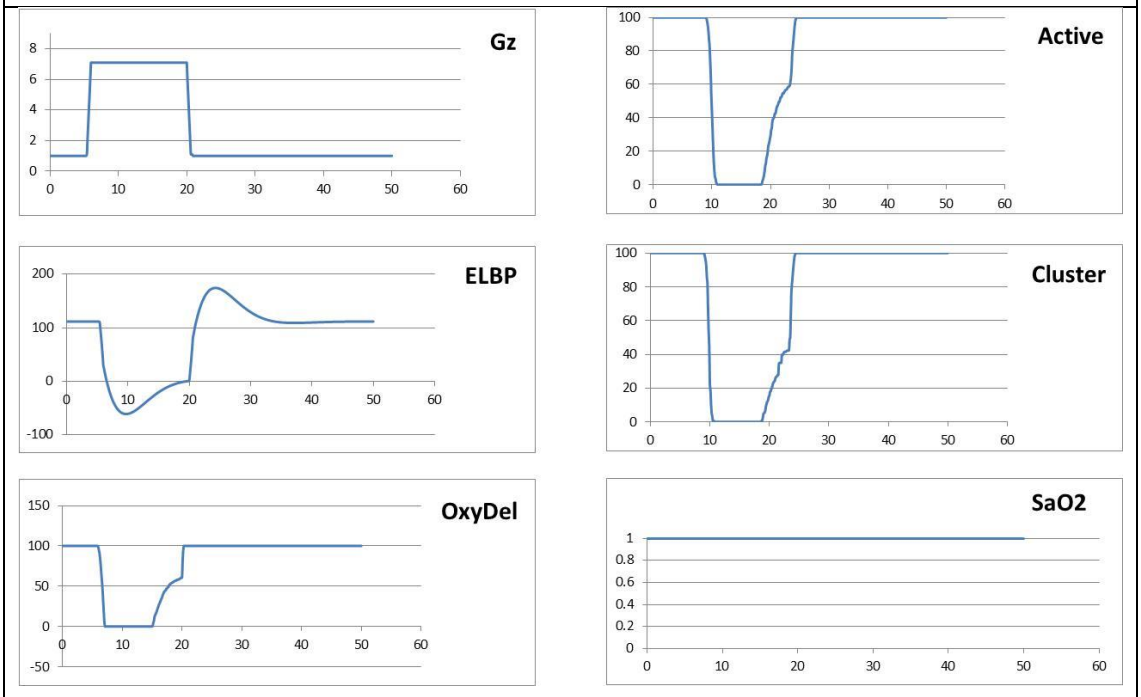
Table 5 Summary Simulation Results

"Off" threshold	Impairment Onset (sec)	Impairment Full Development (sec)	Unconsciousness (sec)
40,000 feet			
0.5	27.4	32.4	-
0.6	16.7	19.5	-
0.7	11.6	13.4	41.1
0.8	4.9	6.9	49.5
7 Gz			
0.5	9	9	10.9
0.6	8.5	8.5	10.3
0.7	8.2	8.2	10.4
0.8	7.7	7.7	10.3

Figure 11 through Figure 14 shows the time history response while varying the mean "off" threshold for both the 40,000 feet and 7Gz exposures.

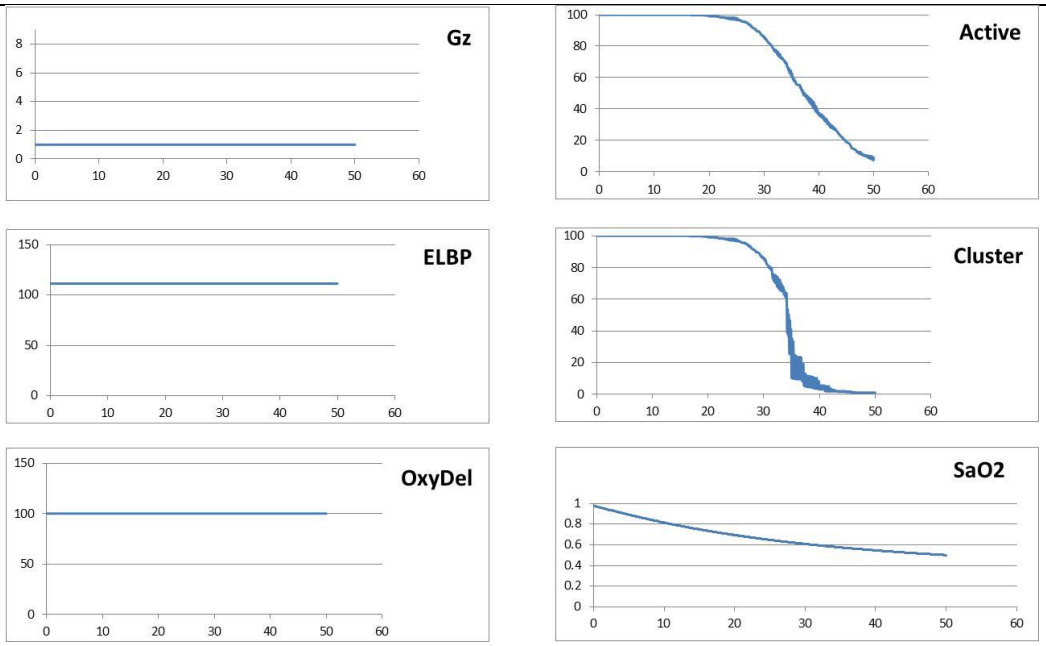


40,000 feet

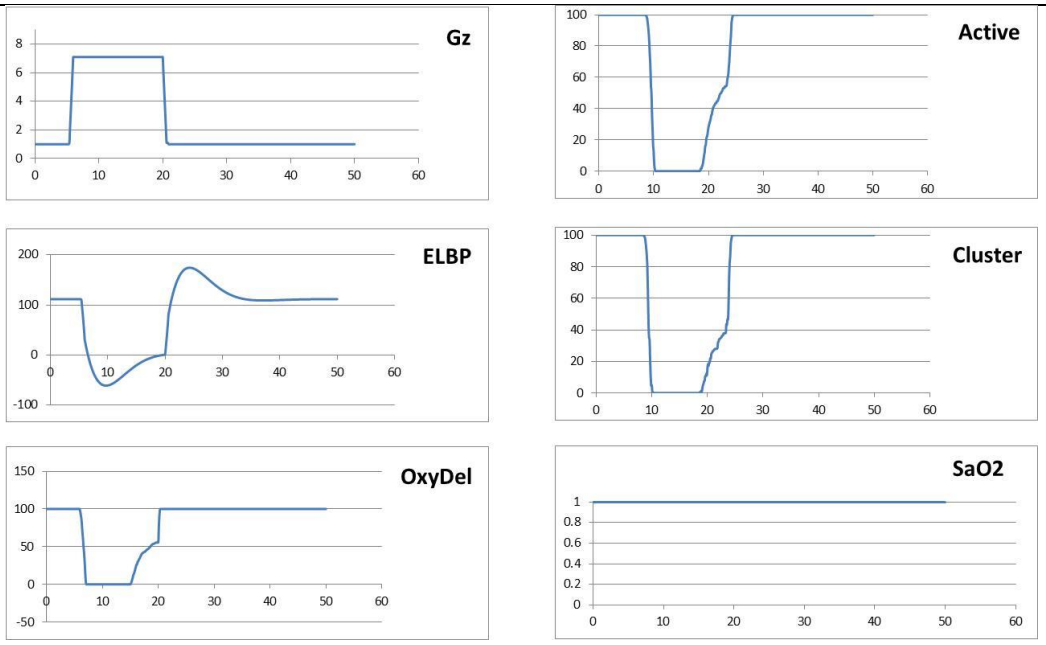


7Gz

Figure 11 Model response at 0.5 threshold

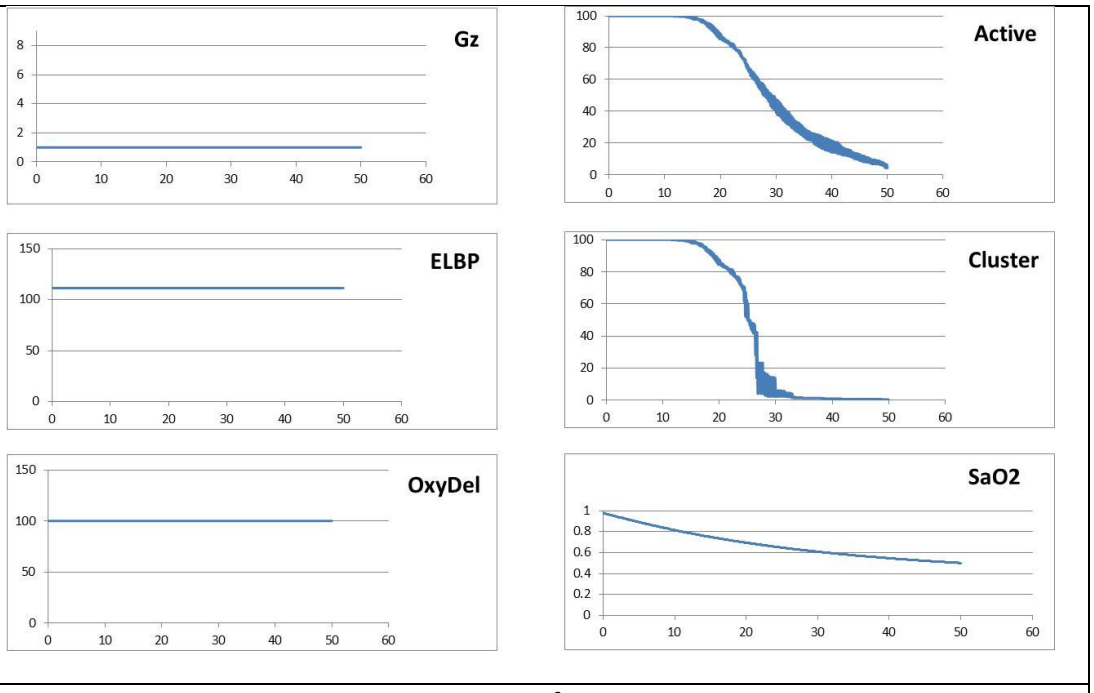


40,000 feet

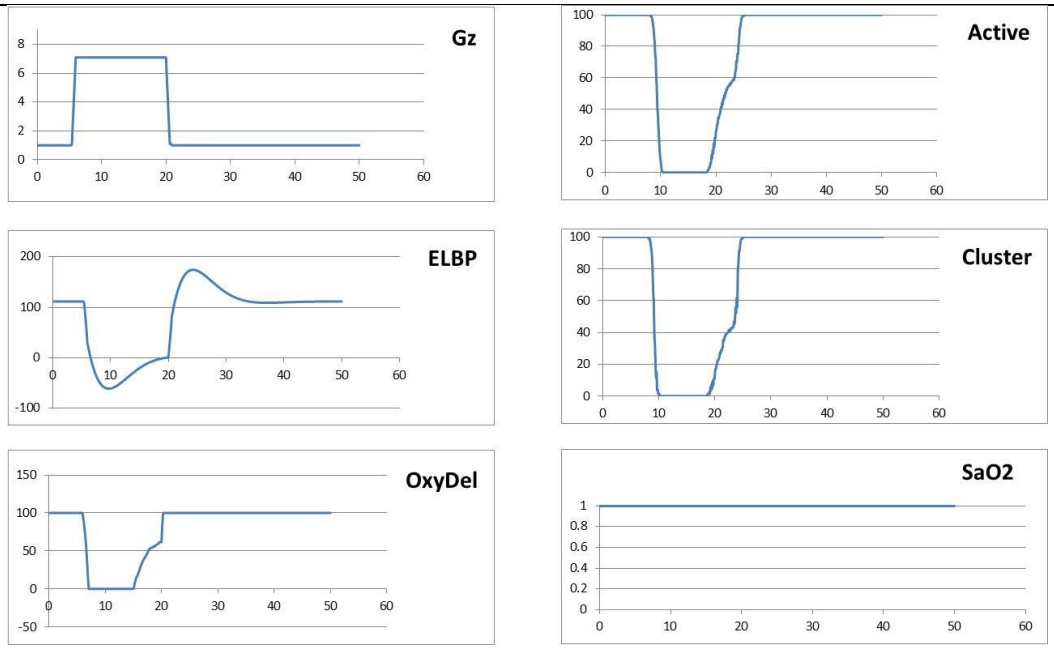


7Gz

Figure 12 Model response at 0.6 threshold

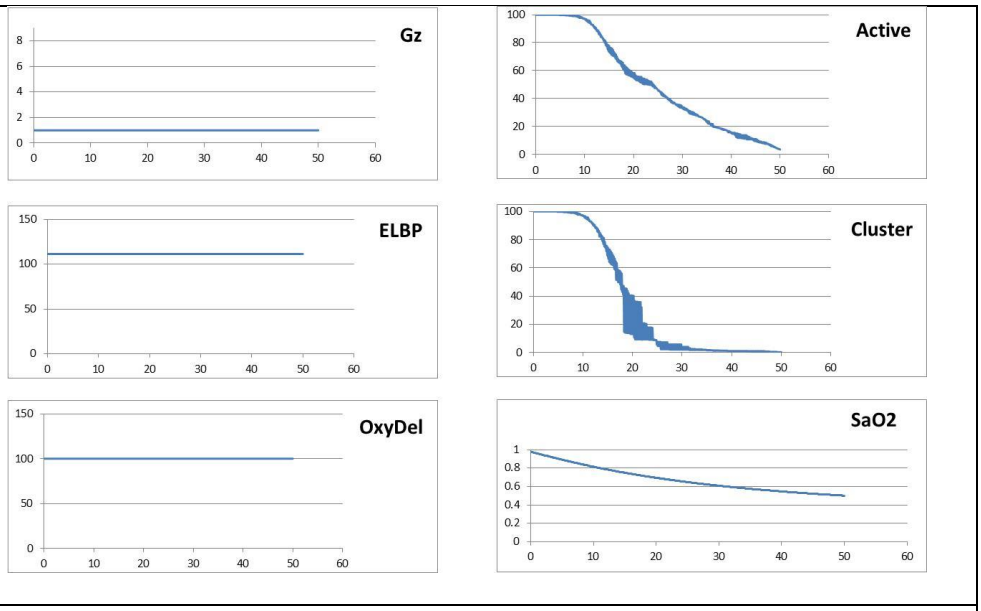


40,000 feet

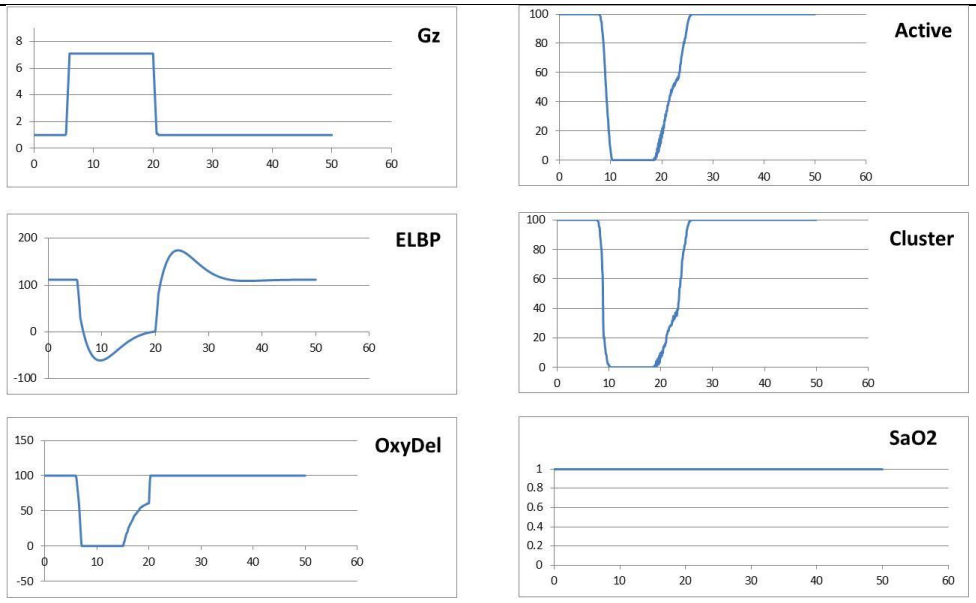


7Gz

Figure 13 Model response at 0.7 threshold



40,000 feet



7Gz

Figure 14 Model response at 0.8 threshold

Both test conditions would be considered to induce unconsciousness in rapid fashion in less than or equal to 10 seconds given an initial subject seated, in a non-working condition. Increasing the mean "off" threshold lowers the impairment times for the hypoxia case but unconsciousness prediction is elusive

owing the likelihood that a connection still exists within the matrix. This can be improved unless we determine that the onset of impairment prediction is sufficient for our usage. For the acceleration case, the onset and development of full impairment are the same and times decrease as the threshold is raised. Unconsciousness is predicted and the threshold change shows little effect on the time predictions.

The combination of the 40,000 feet and 7Gz exposures were simulated and shown in Figure 15.

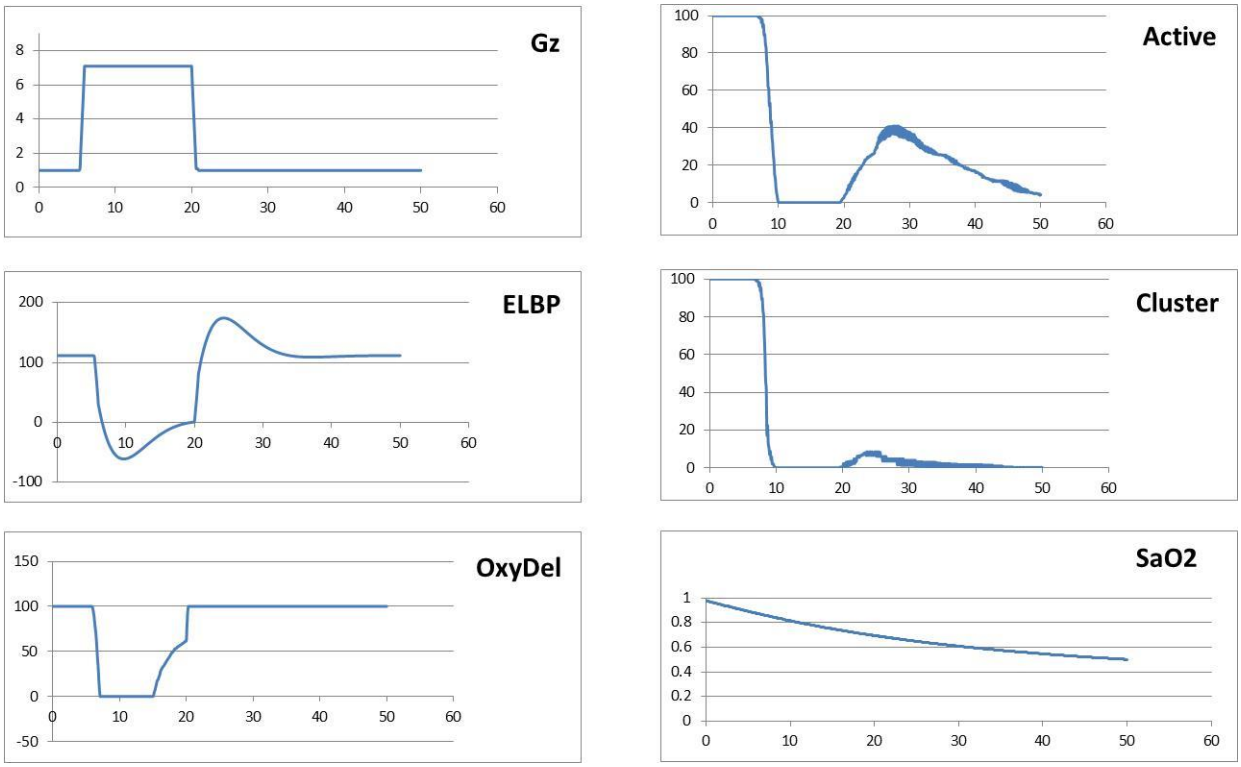


Figure 15 Combination of altitude and acceleration exposures

The onset and full development of impairment was 6.8 seconds and unconsciousness occurred at 10 seconds. After G offset from 7Gz, temporary recovery to impaired state was predicted but oscillated between impaired and unconscious 11 seconds after G offset through to the end of the simulation.

Preliminary HumMod model runs have been conducted to examine whether an SaO_2 based utilization function can be generated for use in conjunction with the unconsciousness model to cover longer, less extreme exposures to altitude while seated and during working activity such as walking an running. Walking or running at high terrestrial altitudes generally results in HumMod indicated muscle fatigue early on, which may indeed be correct. A mission profile needs to be developed that reflect change in altitude, pace and grade to be more realistic.

These results are encouraging for the utilization of the reduced model in the prediction of an abrupt exposure to an unconsciousness inducing exposure. Further adjustment of model parameters should bring abrupt altitude unconsciousness in line with abrupt acceleration unconsciousness predictions.

3.3.3 Task 3c – Determine Model Deficiencies - Other

This task is scheduled to begin in December 2013/January 2014.

3.4 Task 4 – BETA Model Software Development/Definition

This task is scheduled to begin January 2014.

3.5 Task 5 – (Option) – Concept System Refinement

This option has not been exercised. This task is scheduled to begin June 2014.

3.6 Task 6 - Deliverables

See Section 5.2 below.

4.0 Financial Progress

The total base budget for the HAMS program is $385K plus an option of $71K. The contractually obligated amount in FY2013 towards the total budget is $170K. Costs incurred to date for this performance period are $159.5K. The remaining budget is $10.5K. Athena GTX has slowed spending for October 2013 and plans to slow spending for November 2013 to conserve funding while we are waiting for FY2014 funding for the remainder of the program.

We project that we will have exhausted the current funding by the end of November 2013. If funding is secured for the remainder of the program the estimate to complete remains at the original budget for the program ($385K plus an option of $71K if this option is exercised).

The tables below summarized the costs incurred to date against the current funding level of $170K and the FY 2013 benchmarks based on the full FY 2013 contract value of 230K. A more detailed spread sheet has been included in the Appendix, Section 9.2.

4.1 Current Funding ($170K)

Month	Plan (%) *	Actual (%)	Remaining (%)	Comments
AUG	41	58	42	Additional funding will be needed in NOV to fulfill SOW expectations.
SEP	85	81	19	Additional funding will be needed in NOV to fulfill SOW expectations.
OCT	103	94	6	Additional funding will be needed in NOV to fulfill SOW expectations.
NOV	117			
DEC	128			
JAN	135			

* Plan % in this column is based on FY13 funding budget 230K as negotiated in the cost proposal with partial funding of $170K applied.

4.2 Benchmarks for FY13 Funding ($230K)

Month	HAMS Projected (%)	ONR Benchmarks FY13 Funding (%)	HAMS Actual (%)	Benchmark Delta (%)	Comments
AUG	31	49	43	-6	
SEP	63	56	60	+4	
OCT	76	58	69	+11	
NOV	86	63			
DEC	95	68			
JAN	100	73			

5.0 Schedule and Deliverables

5.1 Schedule

Tasks	CY 2013												CY 2014											
	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	APr	May	Jun	Jul
1. Preliminary Research and Documentation																								
2. Develop Parametric Predictive Models																								
3. Algorithm Development and Refinement																								
4. BETA Model Software Development/Definition																								
5. Concept System Refinement (Option)																								
6. Deliverables																								
Monthly Updates																								
Quarterly Reports																								
Final Report																								
Beta Software																								
Trade-off & Preliminary Specification (Option)																								

Progress/Completed
Planned

5.2 Deliverables

5.2.1 Monthly Updates

Three Monthly updates have been submitted to ONR for August, September and October of 2013.

5.2.2 Quarterly Reports

The first quarterly report for the period July 24, 2013 to October 31, 2013 has been submitted to ONR.

5.2.3 Final Report

Not due until May 2014.

5.2.4 BETA Software

Not due until May 2014.

5.2.5 Option – Trade-off Analysis and Preliminary Specification

This option has not been exercised.

6.0 Conclusion

The Hypoxia Monitoring, Alert and Mitigation System (HAMS) program is progressing as expected slightly ahead of schedule with no technical issues to report. Work has begun on Tasks 1, 2 and 3. Task 4 begins in January 2014 and the Task 5 option (not yet exercised) would begin in June 2014.

Partial FY2013 program funding remains an issue, but additional funds are expected in November 2013 to continue the effort without significant impact to the program.

The concentrated effort on the literature search activity (Task 1) has been completed with moderate success. Reasonably so, this task really never ends as new works constantly will be published or become available through professional connections. A File Transfer Protocol (FTP) site has been created to share references and data among the team members and Office of Naval Research (ONR). The literature review to date has provided useful background information and general concepts, but again as expected, no tangible validation data or definitive cognitive endpoints. The Reduced Oxygen Breathing Device (ROBD) data provided by NAVAIR will likely provide the best basis for establishing algorithm threshold limits for HAMS. Consideration for possible impacts to the ANS on testing with ROBD and true altitude hypoxia will continue to be studied.

The baseline parametric hypoxia modeling effort (Task 2) to predict $\%O_2$ saturation, aircrew state, alveolar pressure of oxygen (PaO_2) and alveolar pressure of carbon dioxide ($PaCO_2$) originally programmed in MATLAB/SIMULINK has been converted over to the C programming language. This will allow the algorithm to eventually run on a micro-controller. Verification of the code conversion is underway. This work is ahead of plans and is a key part of the product of the Phase 1 HAMS efforts.

The initial conversion of the United States Navy (USN) Consciousness Model (Task 3) has shown positive results and it appears that it will be possible to reduce the model to a size and complexity that will run on a modest microcontroller. The addition of a hypoxia component to the acceleration component of the model is underway.

7.0 Recommendations

The contractor feels that end-user inputs to the program now are key to ensuring continuation of the funding for HAMS in this sequestration era and progression to a Phase 2 funded effort. As such we support and will continue to provide relevant non-proprietary information for any and all briefings to user groups. If the USN desires the contractor to do such briefings to end users or to brief the ONR on programs such as mini-Medic® and Hammerhead™, potential precursor electronics development programs, it is in our best interest to do so. Previous works at the contracting team have benefitted tremendously from end-users participating in design and development activities.

Finally, we are encouraged that the ONR continues to pursue the remaining funding on Phase 1 in a timely manner to keep the team together.

8.0 References

Not Applicable. See Section 3.1 and 9.1 for literature review results relevant to HAMS.

9.0 Appendix

9.1 Task 1: Preliminary Research and Documentation

9.1.1 Additional Literature Search Results – Abstracts Only

The literature review results are included for completeness.

Andersson, J., Linér, M., Rünow, E., Schagatay, E. (2002). Diving response and arterial oxygen saturation during apnea and exercise in breath-hold divers. *Journal of Applied Physiology.* 93:882-886.

This study addressed the effects of apnea in air and apnea with face immersion in cold water (10°C) on the diving response and arterial oxygen saturation during dynamic exercise. Eight trained breath-hold divers performed steady state exercise on a cycle ergometer at 100 W. During exercise, each subject performed 30-s apneas in air and 30-s apneas with face immersion. The heart rate and arterial oxygen saturation decreased and blood pressure increased during the apneas. Compared with apneas in air, apneas with face immersion augmented the heart rate reduction from 21 to 33% (P <0.001) and the blood pressure increase from 34 to 42% (P < 0.05). The reduction in arterial oxygen saturation from eupneic control was 6.8% during apneas in air and 5.2% during apneas with face immersion (P < 0.05). The results indicate that augmentation of the diving response slows down the depletion of the lung oxygen store, possibly associated with a larger reduction in peripheral venous oxygen stores and increased anaerobiosis. This mechanism delays the fall in alveolar and arterial PO2 and, thereby, the development of hypoxia in vital organs. Accordingly, we conclude that the human diving response has an oxygen-conserving effect during exercise.

Bailey, D., Bartsch, P., Knauth, M., Baumgartner, R. (2009). Emerging concepts in acute mountain sickness and high-altitude cerebral edema: from the molecular to the morphological. *Cellular and Molecular Life Sciences.*

Acute mountain sickness (AMS) is a neurological disorder that typically affects mountaineers who ascend to high altitude. The symptoms have traditionally been ascribed to intracranial hypertension caused by extracellular vasogenic edematous brain swelling subsequent to mechanical disruption of the blood–brain barrier in hypoxia. However, recent diffusion-weighted magnetic resonance imaging studies have

identified mild astrocytic swelling caused by a net redistribution of fluid from the ''hypoxia-primed'' extracellular space to the intracellular space without any evidence for further barrier disruption or additional increment in brain edema, swelling or pressure. These findings and the observation of minor vasogenic edema present in individuals with and without AMS suggest that the symptoms are not explained by cerebral edema. This has led to a re-evaluation of the relevant pathogenic events with a specific focus on free radicals and their interaction with the trigeminovascular system. (Part of a multi-author review.)

Brown, J., Grocott, M. (2013) Humans at Altitude: Physiology and Pathophysiology. *Continuing Education in Anesthesia, Critical Care & Pain j*. Volume 13 Number 1.

This article describes the physiological challenge associated with exposure to environmental hypoxia at high altitude along with adaptive (acclimatization) and pathological (acute high altitude illness) responses to this challenge.

Gallagher, S., Hackett, P. (2004). High-Altitude Illness. *Emergency Medical Clinics of North America.* (2):329-55, viii.

Travel to a high altitude requires that the human body acclimatize to hypobaric hypoxia. Failure to acclimatize results in three common but preventable maladies known collectively as high-altitude illness: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). Capillary leakage in the brain (AMS/HACE) or lungs (HAPE) accounts for these syndromes. The morbidity and mortality associated with high-altitude illness are significant and unfortunate, given they are preventable. Practitioners working in or advising those traveling to a high altitude must be familiar with the early recognition of symptoms, prompt and appropriate therapy, and proper preventative measures for high-altitude illness.

GAO, M., WANG, R., JIAYONG3, Z., LIU, Y., SUN, G. (2013). NT-ProBNP levels are moderately increased in acute high-altitude pulmonary edema. *EXPERIMENTAL AND THERAPEUTIC MEDICINE.* 5: 1434-1438.

The aim of the present study was to investigate the effect of B-type natriuretic peptides (BNPs) in acute high-altitude pulmonary edema (HAPE). The study enrolled 46 subjects from lowland Han, including 33 individuals who had acutely ascended to a high altitude (21 individuals with HAPE as the case group and 12 individuals without HAPE as the high-altitude control group) and 13 healthy normal residents as the plain control group. The serum concentrations of N-terminal probrain natriuretic peptide (NT-proBNP), erythropoietin (EPO), vascular endothelial growth factor (VEGF) and nitric oxide (NO) were measured. There were significant differences in the serum concentrations of NT-ProBNP, NO, VEGF and EPO among

the three groups. The serum concentrations of NT-ProBNP, EPO and VEGF were significantly higher in the HAPE patients and high-altitude control individuals than those of the plain group. No significant differences were identified between the HAPE patients and the high-altitude control group. In contrast to these three parameters, the serum concentrations of NO in the high-altitude control group were significantly higher than those of the HAPE patients and the plain group, while there were no significant differences in the serum concentrations of NO between the HAPE patients and the plain group. Furthermore, serum concentrations of NT-ProBNP and EPO were significantly reduced following treatment in the HAPE patients, however, no significant changes were identified in VEGF or NO concentrations. BNPs are increased in HAPE with severe hypoxia and right ventricular overload, but are decreased subsequent to treatment. BNPs may therefore be a potential biomarker for the diagnosis and prognosis of HAPE.

Golja, P., Kacin, A., Tipton, M., Eiken, O., Mekjavic, I.(2004). Hypoxia increases the cutaneous threshold for the sensation of cold. *European Journal of Applied Physiology*. 92(1-2):62-8.

Cutaneous temperature sensitivity was tested in 13 male subjects prior to, during and after they breathed either a hypocapnic hypoxic (HH), or a normocapnic hypoxic (NH) breathing mixture containing 10% oxygen in nitrogen. Normocapnia was maintained by adding carbon dioxide to the inspired gas mixture. Cutaneous thresholds for thermal sensation were determined by a thermo sensitivity testing device positioned on the plantar side of the first two toes on one leg. Heart rate, haemoglobin saturation, skin temperature at four sites (arm, chest, thigh, calf) and adapting temperature of the skin (T(ad); degrees centigrade), i.e. the temperature of the toe skin preceding a thermo sensitivity test, were measured at minute intervals. Tympanic temperature (T(ty); degrees centigrade) was measured prior to the initial normoxic thermo sensitivity test, during the hypoxic exposure and after the completion of the final normoxic thermo sensitivity test. End-tidal carbon dioxide fraction and minute inspiratory volume were measured continuously during the hypoxic exposure. Ambient temperature, T(ty), T(ad) and mean skin temperature remained similar in both experimental conditions. Cutaneous sensitivity to cold decreased during both HH ($P<0.001$) and NH conditions ($P<0.001$) as compared with the tests undertaken pre- and post-hypoxia. No similar effect was observed for cutaneous sensitivity to warmth. The results of the present study suggest that sensitivity to cold decreases during the hypoxic exposure due to the effects associated with hypoxia rather than hypocapnia. Such alteration in thermal perception may affect the individual's perception of thermal comfort and consequently attenuate thermoregulatory behaviour during cold exposure at altitude.

Heiner, M., Sriram, K. (2010). Structural analysis to determine the core of hypoxia response network. *PLoS One.* 5(1).

The advent of sophisticated molecular biology techniques allows to deduce the structure of complex biological networks. However, networks tend to be huge and impose computational challenges on traditional mathematical analysis due to their high dimension and lack of reliable kinetic data. To overcome this problem, complex biological networks are decomposed into modules that are assumed to capture essential aspects of the full network's dynamics. The question that begs for an answer is how to identify the core that is representative of a network's dynamics, its function and robustness. One of the powerful methods to probe into the structure of a network is Petri net analysis. Petri nets support network visualization and execution. They are also equipped with sound mathematical and formal reasoning based on which a network can be decomposed into modules. The structural analysis provides insight into the robustness and facilitates the identification of fragile nodes. The application of these techniques to a previously proposed hypoxia control network reveals three functional modules responsible for degrading the hypoxia-inducible factor (HIF). Interestingly, the structural analysis identifies superfluous network parts and suggests that the reversibility of the reactions are not important for the essential functionality. The core network is determined to be the union of the three reduced individual modules. The structural analysis results are confirmed by numerical integration of the differential equations induced by the individual modules as well as their composition. The structural analysis leads also to a coarse network structure highlighting the structural principles inherent in the three functional modules. Importantly, our analysis identifies the fragile node in this robust network without which the switch-like behavior is shown to be completely absent.

Jensen, L., Onyskiw, J., Prasad, N. (1998). Meta-Analysis of Arterial Oxygen Saturation Monitoring by Pulse Oximetry in Adults. *Heart & Lung.* 27: 387-408.

The purposes of the study were to: (1) describe the aggregate strength of the relationship of arterial oxygen saturation as measured by pulse oximetry with the standard of arterial blood gas analysis as measured by co-oximetry, (2) examine how various factors affect this relationship, and (3) describe an aggregate estimate of the bias and precision between oxygen saturation as measured by pulse oximetry and the standard in vitro measures.

Karinen, H., Peltonen, J., Kahonen, M., Tikkanen, H. (2010). Prediction of Acute Mountain Sickness by Monitoring Arterial Oxygen Saturation During Ascent. *High Altitude Medicine & Biology.* 11:325–332.

Acute mountain sickness (AMS) is a common problem while ascending at high altitude. AMS may progress rapidly to fatal results if the acclimatization process fails or symptoms are neglected and the ascent continues. Extensively reduced arterial oxygen saturation at rest (R-Spo2) has been proposed as an indicator of inadequate acclimatization and impending AMS. We hypothesized that climbers less likely to develop AMS on further ascent would have higher Spo2 immediately after exercise (Ex-Spo2) at high altitudes than their counterparts and that these post exercise measurements would provide additional value for resting measurements to plan safe ascent. The study was conducted during eight expeditions with 83 ascents. We measured R-Spo2 and Ex-Spo2 after moderate daily exercise [50m walking, target heart rate (HR) 150 bpm] at altitudes of 2400 to 5300m during ascent. The Lake Louise Questionnaire was used in the diagnosis of AMS. Ex-Spo2 was lower at all altitudes among those climbers suffering from AMS during the expeditions than among those climbers who did not get AMS at any altitude during the expeditions. Reduced R-Spo2 and Ex-Spo2 measured at altitudes of 3500 and 4300m seem to predict impending AMS at altitudes of 4300m ($p<0.05$ and $p<0.01$) and 5300m (both $p<0.01$). Elevated resting HR did not predict impending AMS at these altitudes. Better aerobic capacity, younger age, and higher body mass index (BMI) were also associated with AMS (all $p<0.01$). In conclusion, those climbers who successfully maintain their oxygen saturation at rest, especially during exercise, most likely do not develop AMS. The results suggest that daily evaluation of Spo2 during ascent both at rest and during exercise can help to identify a population that does well at altitude.

Katayama, K., Fujita, O., Lemitsu, M., Kawana, H., Iwamoto, E., Saito, M., Ishida, K. (2013). The effect of acute exercise in hypoxia on flow-mediated vasodilation. *Eur J Appl Physiol*. 113:349–357.

The purpose of this study was to clarify the effect of acute exercise in hypoxia on flow-mediated vasodilation (FMD). Eight males participated in this study. Two maximal exercise tests were performed using arm cycle ergometry to estimate peak oxygen uptake _V_ O2peak_ while breathing normoxic [inspired O2 fraction (FIO2) = 0.21] or hypoxic (FIO2 = 0.12) gas mixtures. Next, subjects performed submaximal exercise at the same relative exercise intensity 30% _V _ O2peak_ in normoxia or hypoxia for 30 min. Before (Pre) and after exercise (Post 5, 30, and 60 min), brachial artery FMD was measured during reactive hyperemia by ultrasound under normoxic conditions. FMD was estimated as the percent (%) rise in the peak diameter from the baseline value at prior occlusion at each FMD measurement %FMD). The area under the curve for the shear rate stimulus (SRAUC) was calculated in each measurement, and each %FMD value was normalized to SRAUC (normalized FMD). %FMD and normalized FMD decreased significantly (P\0.05) immediately after exercise in both condition (mean ± SE, FMD, normoxic trial, Pre: 8.85 ± 0.58 %, Post 5:-0.01 ±1.30 %, hypoxic trial, Pre: 8.84 ± 0.63 %, Post 5: 2.56 ± 0.83 %). At Post 30 and 60, %FMD and normalized FMD returned gradually to pre-exercise levels in both trials (FMD, normoxic trial, Post 30: 1.51 ± 0.68 %, Post 60: 2.99 ± 0.79 %; hypoxic trial, Post 30: 4.57 ± 0.78 %, Post 60: 6.15 ±

1.20 %). %FMD and normalized FMD following hypoxic exercise (at Post 5, 30, and 60) were significantly (P\0.05) higher than after normoxic exercise. These results suggest that aerobic exercise in hypoxia has a significant impact on endothelial-mediated vasodilation.

Levett, D., Fernandez, B., Riley, H., Martin, D., Mitchell, K., Leckstrom, C., Ince, C., Whipp, B., Mythen, M., Montgomery, H., Grocott, M., Feelisch, M. (2011). The role of nitrogen oxides in human adaptation to hypoxia. *SCIENTIFIC REPORTS*. 1: 109.

Lowland residents adapt to the reduced oxygen availability at high altitude through a process known as acclimatization, but the molecular changes underpinning these functional alterations are not well-understood. Using an integrated biochemical/whole-body physiology approach we here show that plasma biomarkers of NO production (nitrite, nitrate) and activity (cGMP) are elevated on acclimatization to high altitude while S-nitrosothiols are initially consumed, suggesting multiple nitrogen oxides contribute to improve hypoxia tolerance by enhancing NO availability. Unexpectedly, oxygen cost of exercise and mechanical efficiency remain unchanged with ascent while microvascular blood flow correlates inversely with nitrite. Our results suggest that NO is an integral part of the human physiological response to hypoxia. These findings may be of relevance not only to healthy subjects exposed to high altitude but also to patients in whom oxygen availability is limited through disease affecting the heart, lung or vasculature, and to the field of developmental biology.

Netzer, N., Strohl, K., Faulhaber, M., Gatterer, H., Burtscher, M. (2013). Hypoxia-Related Altitude Illnesses. *Journal of Travel Medicine.* Volume 20 (Issue 4): 247–255.

Acute mountain sickness (AMS) represents the most common and usually benign illness, which however can rapidly progress to the more severe and potentially fatal forms of high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE) 2, 3, 6, 7. As altitude medicine specialists are rare, the primary care practitioner has to provide advice to the novice traveler. High altitudes may be associated with many conditions not related to hypoxia per se, e.g., cold, UV radiation, physical exertion, infections, and trauma, which are not covered in this article. For respective information, the interested reader is referred to the article by Boggild and colleagues 8. The purpose of this review is to introduce the travel health provider to basic concepts of hypoxia-related high-altitude conditions and to provide state-of-the art recommendations for prevention and therapy of high-altitude illnesses.

Parell, J., Becker, G. (1993). Inner ear barotrauma in scuba divers. A long-term follow-up after continued diving. *Arch Otolaryngol Head Neck Surg.* 119(4):455-7.

Divers who suffer inner ear barotrauma are usually counseled to permanently avoid diving, reasoning that the injured inner ear is at increased risk of further damage. Twenty patients who suffered inner ear barotrauma while diving, but continued to dive against medical advice, were assessed on an interim basis for 1 to 12 years. As difficulty equalizing the ears during the barotraumatic event was a universal finding, prior to resuming diving, all patients were reinstructed on methods of maximizing eustachian tube function. No further deterioration of cochleo-vestibular function was noted. Based on these preliminary results, we conclude that recommending no further diving after inner ear barotrauma may be unnecessarily restrictive.

Penneys, R. Thomas, C. (1950). The Relationship between the Arterial Oxygen Saturation and the Cardiovascular Response to Induced Anoxemia in Normal Young Adults. *American Heart Association: Circulation.* 1:415-425.

At the present time the most widely used method of studying the effect of induced anoxemia on the cardiovascular system consists of giving the subjects low oxygen gas (usually 10 per cent) inhalation for approximately twenty minutes and making observations during this period. In previous communications the variability of the degree of anoxemia, as measured by the blood arterial oxygen saturation, during inhalation of a gas of fixed low oxygen concentration was pointed out. The physiologic importance of standardizing the induced anoxemia test of cardiovascular function according to the level of the arterial oxygen saturation was discussed and a method of inducing and maintaining a constant degree of anoxemia by administering a gas of variable oxygen concentration was described. In one of these reports' the nature of the cardiovascular response of a small group of young men at levels of 85, 80, and 75 per cent arterial oxygen saturation was presented. It is the purpose of this report to give a detailed description and analysis of the effect of anoxemia upon the heart rate, blood pressure, and electrocardiogram at levels of 80, 75, and 70 per cent arterial saturation in a substantial number of normal young adults.

Ren, Y., Cui, F. Lei, Y., Fu, Z., Wu, Z., Cui, B. (2012). High-Altitude Pulmonary Edema Is Associated With Coagulation and Fibrinolytic Abnormalities. *The American Journal of the Medical Sciences*.

High-altitude pulmonary edema (HAPE) can develop in unacclimatized persons after acute ascent to high altitude and is associated with fibrinolytic and coagulation abnormalities. The authors investigated whether fibrinolytic and coagulation abnormalities were associated with the severity of HAPE. Methods: Sixty-one patients who developed HAPE after acute ascent to altitudes above 3600 m were recruited. Twenty unacclimatized controls who acutely ascended to the same altitude and 20 acclimatized inhabitants served as controls. Tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) levels were measured using chromogenic substrate assays. Plasma fibrinogen concentration was determined by the sodium sulphite fractionation method. The concentrations of fibrin/fibrinogen

degradation products (FDP) and D-dimer were measured by enzyme linked immunosorbent assay. Results: The plasma concentrations of D-dimer, fibrinogen, FDP and t-PA and PAI-1 were significantly higher in patients with HAPE than controls. In addition, these abnormalities were correlated with the severity of HAPE. The plasma concentrations of D-dimer and fibrinogen recovered to normal upon recovery from HAPE while t-PA, PAI-1 and FDP levels in HAPE patients still remained significantly increased over those of unacclimatized controls. Conclusion: The development of HAPE is associated with abnormalities in the fibrinolysis and coagulation system, and these abnormalities correlate with the severity of HAPE.

Romer, L., Haverkamp, H., Amann, M., Lovering, A., Pegelow, D., Dempsey, J. (2007). Effect of Acute Severe Hypoxia on Peripheral Fatigue and Endurance Capacity in Healthy Humans. *American Journal of Physiology. Regulatory, Integrative, Comparative Physiology.* 292(1):R598-606.

We hypothesized that severe hypoxia limits exercise performance via decreased contractility of limb locomotor muscles. Nine male subjects [mean +/- SE maximum O(2) uptake (Vo(2 max)) = 56.5 +/- 2.7 ml x kg(-1) x min(-1)] cycled at > or =90% Vo(2 max) to exhaustion in normoxia [NORM-EXH; inspired O(2) fraction (Fi(O(2))) = 0.21, arterial O(2) saturation (Sp(O(2))) = 93 +/- 1%] and hypoxia (HYPOX-EXH; Fi(O(2)) = 0.13, Sp(O(2)) = 76 +/- 1%). The subjects also exercised in normoxia for a time equal to that achieved in hypoxia (NORM-CTRL; Sp(O(2)) = 96 +/- 1%). Quadriceps twitch force, in response to supramaximal single (non-potentiated and potentiated 1 Hz) and paired magnetic stimuli of the femoral nerve (10-100 Hz), was assessed pre- and at 2.5, 35, and 70 min post exercise. Hypoxia exacerbated exercise-induced peripheral fatigue, as evidenced by a greater decrease in potentiated twitch force in HYPOX-EXH vs. NORM-CTRL (-39 +/- 4 vs. -24 +/- 3%, P < 0.01). Time to exhaustion was reduced by more than two-thirds in HYPOX-EXH vs. NORM-EXH (4.2 +/- 0.5 vs. 13.4 +/- 0.8 min, P < 0.01); however, peripheral fatigue was not different in HYPOX-EXH vs. NORM-EXH (-34 +/- 4 vs. -39 +/- 4%, P > 0.05). Blood lactate concentration and perceptions of limb discomfort were higher throughout HYPOX-EXH vs. NORM-CTRL but were not different at end-exercise in HYPOX-EXH vs. NORM-EXH. We conclude that severe hypoxia exacerbates peripheral fatigue of limb locomotor muscles and that this effect may contribute, in part, to the early termination of exercise.

Smith, A. (2008). Hypoxia symptoms in military aircrew: long-term recall vs. acute experience in training. *Aviation Space Environmental Medicine*. 79:54 – 7.

It has been reported that many aircrew who experience hypoxia-related incidents are able to recognize hypoxia because of similarity to symptoms they experienced during hypoxia awareness training. This study aimed to explore the degree of similarity between symptoms reported after acute hypoxia and those remembered from previous hypoxia awareness training.

Stein, J., Ellsworth, M. (1993). Capillary oxygen transport during severe hypoxia: role of hemoglobin oxygen affinity. *Journal of Applied Physiology.* 75(4):1601-7.

The efficacy of an increased hemoglobin oxygen affinity [decreased oxygen half-saturation pressure of hemoglobin (P50)] on capillary oxygen transport was evaluated in the hamster retractor muscle under conditions of a severely limited oxygen supply resulting from the combined effects of a 40% reduction in systemic hematocrit and hypoxic ventilation (inspired oxygen fraction 0.1). Two groups of hamsters were utilized: one with a normal oxygen affinity (untreated; P50 = 26.1 +/- 2.4 Torr) and one with an increased oxygen affinity (treated; P50 = 15.7 +/- 1.4 Torr) induced by the chronic short-term administration of sodium cyanate. Using in vivo video microscopy and image analysis techniques, we determined oxygen saturation and associated hemodynamics at both ends of the capillary network. During hypoxic ventilation, the decrease in oxygen saturation across the network was 3.6% for untreated animals compared with 9.9% for treated animals. During hypoxia, estimated end-capillary PO2 was significantly higher in the untreated animals. These data indicate that, at the capillary level, a decreased P50 is advantageous for tissue oxygenation when oxygen supply is severely compromised, because normal oxygen losses in capillaries are maintained in treated but not in untreated animals. The data are consistent with the presence of a diffusion limitation for oxygen during severe hypoxia in animals with a normal hemoglobin oxygen affinity.

Still, D., Temme, L. (2012). An independent, objective calibration check for the reduced oxygen breathing device. *Aviation, Space Environmental Medicine.* 83(9):902-8.

Normobaric hypoxia, which does not entail an altitude chamber, but reduces the fraction of inspired oxygen (02) by diluting air with nitrogen, is finding increased use. The reduced oxygen breathing device (ROBD-2) is one of several commercial devices for generating such normobaric hypoxia. Reported here are results of a procedure to check the calibration of the ROBD-2 using methods that may be readily available in physiology and psychophysiology facilities.

Tannheimer, M., Hornung, K., Gasche, M., Kuehlmuss, B., Mueller, M., Welsch, H., Landgraf, K., Guger, K., Schmidt, R., Steinacker, J. (2012). Decrease of Asymmetric Dimethylarginine Predicts Acute Mountain Sickness. *Journal of Travel Medicine* 2012; Volume 19 (Issue 6): 338–343.

Each year, 40 million tourists worldwide are at risk of getting acute mountain sickness (AMS), because they travel to altitudes of over 2500 m. As asymmetric dimethylarginine (ADMA) is a nitric oxide synthase (NOS) inhibitor, it should increase pulmonary artery pressure (PAP) and raise the risk of acute mountain sickness and high-altitude pulmonary edema (HAPE).With this in mind, we investigated whether changes in ADMA levels (_-ADMA) at an altitude of 4000m can predict an individual's susceptibility to AMS or HAPE.

Tyler, I., Tantisira, B., Winter, P., Motoyama, E. (1985). Continuous Monitoring of Arterial Oxygen Saturation With Pulse Oximetry during Transfer to the Recovery Room. *Anesth Analg.* 64:1108-12.

The incidence of hypoxemia in the immediate postoperative period was determined using a pulse oximeter for continuous monitoring of arterial oxygen saturation (SaO2) in 95 ASA class I or II adult patients breathing room air during their transfer from the operating room to the recovery room. Hypoxemia was defined as 90% SaO2 (arterial oxygen partial pressure (PaO2) approximately equal to 58 mm Hg). Severe hypoxemia was defined as 85% SaO2 (PaO2 approximately equal to 50 mm Hg). Hypoxemia occurred in 33 (35%) patients; severe hypoxemia occurred in 11 (12%). Postoperative hypoxemia did not correlate significantly with anesthetic agent, age, duration of anesthesia, or level of consciousness. There was a statistically significant correlation (P less than 0.05) between hypoxemia and obesity. All three patients with a history of mild asthma became severely hypoxemic even though none had perioperative evidence of obstructive disease, also a statistically significant (P less than 0.003) finding.

Wagner, D., Knott, J., Fry, J. (2012). Oximetry Fails to Predict Acute Mountain Sickness or Summit Success During a Rapid Ascent to 5640 Meters. *Wilderness & Environmental Medicine.*

The purpose of this study was to determine whether arterial oxygen saturation (SpO2) and heart rate (HR), as measured by a finger pulse oximeter on rapid arrival to 4260 m, could be predictive of acute mountain sickness (AMS) or summit success on a climb to 5640 m.

Weathersby, P., Survanshi, S., Homer, L., Parker, E., Thalmann, E. (1992). Predicting The Time of Occurrence of Decompression Sickness. *Journal of Applied Physiology.* 72: 1541 - 1548.

Probabilistic models and maximum likelihood estimation have been used to predict the occurrence of decompression sickness (DCS). We indicate a means of extending the maximum likelihood parameter estimation procedure to make use of knowledge of the time at which DCS occurs. Two models were compared in fitting a data set of nearly 1,000 exposures, in which MO cases of DCS have known times of symptom onset. The additional information provided by the time at which DCS occurred gave us better estimates of model parameters. It was also possible to discriminate between good models, which predict both the occurrence of DCS and the time at which symptoms occur, and poorer models, which may predict only the overall occurrence. The refined models may be useful in new applications for customizing decompression strategies during complex dives involving various times at several different depths. Conditional probabilities of DCS for such dives may be reckoned as the dive is taking place and the decompression strategy adjusted to circumstance. Some of the mechanistic implications and the assumptions needed for safe application of decompression strategies on the basis of conditional probabilities are discussed.

Westerman, R. (2004).Hypoxia familiarization training by the reduced oxygen breathing method. *Aviation Medicine.* 5: 11-15.

Hypoxia familiarization training demonstrates and measures (1) cardiorespiratory adjustments in healthy volunteers to a simulated altitude of 25000 ft. (7620 m); (2) the spectrum of signs and symptoms accompanying hypoxia; (3) individual variability in susceptibility to hypoxia and oxygen paradox; and (4) time of useful consciousness. Trainees experience the insidious onset and obvious performance decrements resulting from hypoxia. Hypobaric chambers are traditionally used for this purpose, but carry a risk of inducing decompression sickness in trainees. An alternative is the use of low oxygen gas mixtures to simulate breathing conditions at high altitude.

West, J. (2004). The Physiologic Basis of High-Altitude Diseases. *Ann Intern Med. 2004; 141:789-800.*

Many physicians are surprised to learn how many people live, work, and play at high altitude. Some 140 million persons reside at altitudes over 2500 m, mainly in North, Central, and South America; Asia; and eastern Africa (1). Increasingly, people are moving to work at high altitude. For example, there are telescopes at altitudes over 5000 m (2) and mines at over 4500 m (3), and the Golmud–Lhasa railroad being constructed in Tibet will have 30 000 to 50 000 workers at high altitudes, including many who work at more than 4000 m. Skiers, mountaineers, and trekkers go to altitudes of 3000 m to more than 8000 m for recreation, and sudden ascents to high altitude without the benefits of acclimatization are common. All of these groups are prone to high-altitude diseases that sometimes have fatal consequences. In addition, the physiology of hypoxia, which is at the basis of high-altitude medicine, plays an important role in many lung and heart diseases.

Zhou, Qiquan. (2011). Standardization of Methods for Early Diagnosis and On-Site Treatment of High-Altitude Pulmonary Edema. *Hindawi Publishing Corporation, Pulmonary Medicine*.

High-altitude pulmonary edema (HAPE) is a life-threatening disease of high altitude that often affects nonacclimatized apparently healthy individuals who rapidly ascend to high altitude. Early detection, early diagnosis, and early treatment are essential to maintain the safety of people who ascend to high altitude, such as construction workers and tourists. In this paper, I discuss various methods and criteria that can be used for the early diagnosis and prediction of HAPE. I also discuss the preventive strategies and options for on-site treatment. My objective is to improve the understanding of HAPE and to highlight the need for prevention, early diagnosis, and early treatment of HAPE to improve the safety of individuals ascending to high altitude.

9.1.2 Hams File Sharing Management System

To upload files using the Hams File system, you must first register with the system from the home page. After you have registered an approval email will be sent to your account.

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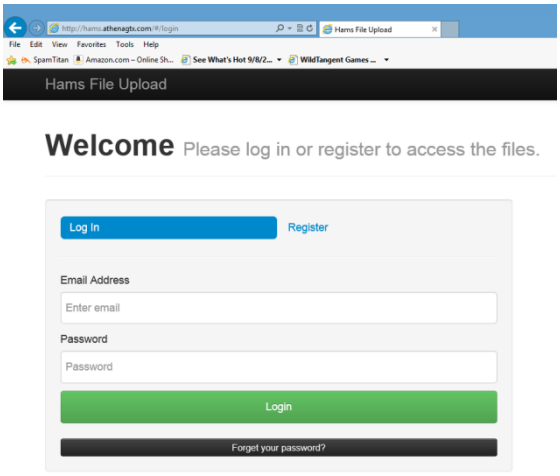
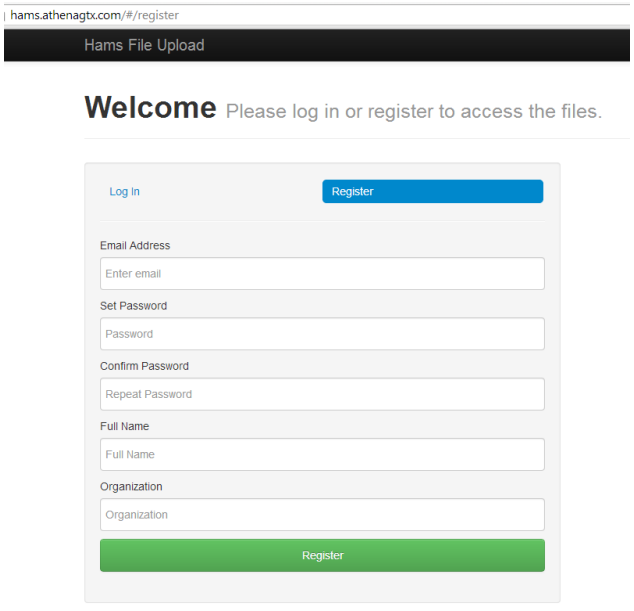


Clicking on **Register** brings you to the registration input screen. Fill in the required information and click the green **"Register"** button. An approval email will be sent to your account.



Once you have been approved, you will be able to log into the system through the home page. Logging into the system will take you to the documents page. Here you will be able to download, delete, upload and search documents and folders.

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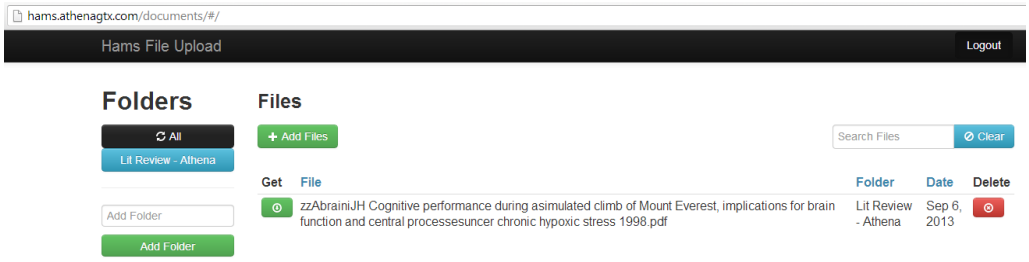

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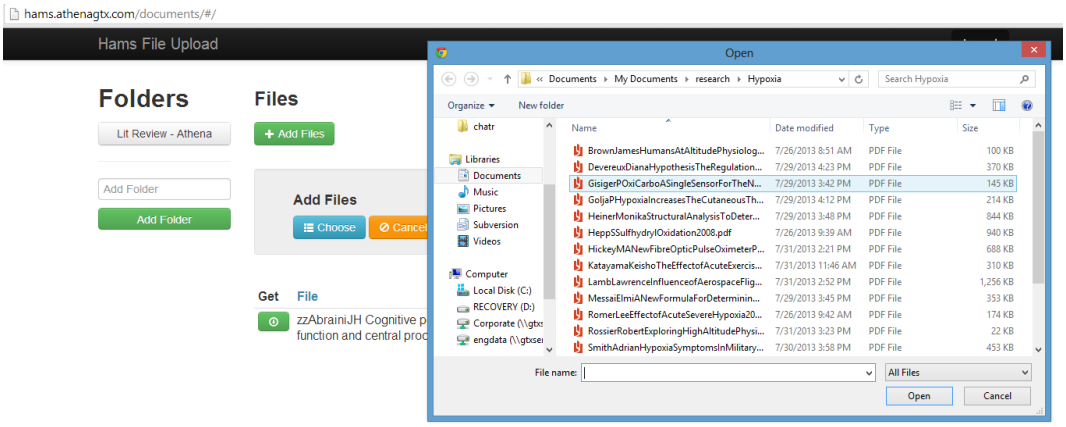
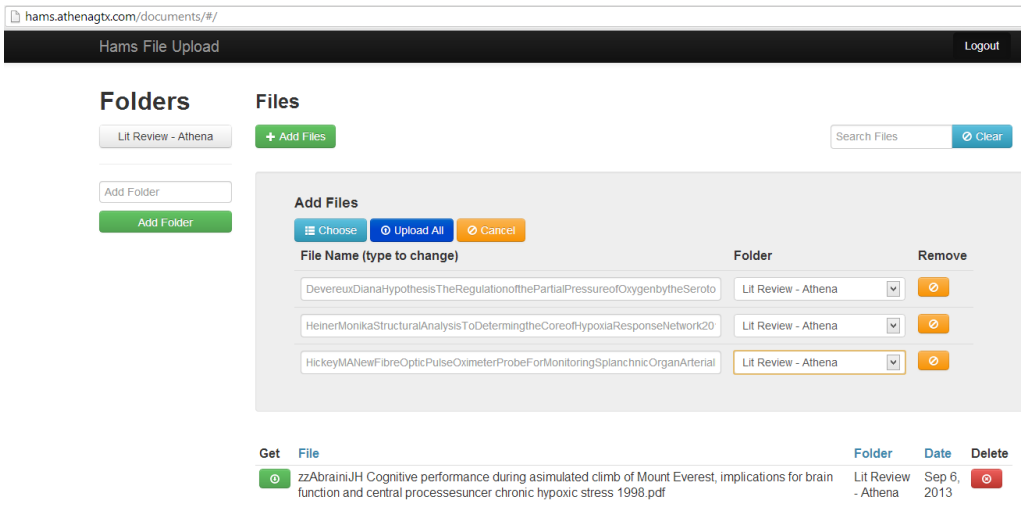


- Then you may change the name of the document you are uploading and select or change the folder. (optional)
- To remove the document(s) select the orange **(Remove)** button to the left of the file.

- Once the files are named and folders are selected click the dark blue "**Upload All**" button.



Note: To upload all the files into a single Folder, select the folder first then select the Choose Button. This will auto populate the folder field in the upload process. This field can be edited if one or more documents selected for upload are to go into a different folder.

9.2 Detailed Financial Spreadsheets (PDF)

H.A.M.S. FUND YEAR 2013 / 2014		EXPENDITURE % BY MONTH based on 170K	58.67%	81.46%	93.78%	93.78%	93.78%	93.78%	93.78%	93.78%	93.78%	93.78%	93.78%	93.78%
CONTRACT# N00014-13-C-0323														
EFFECTIVE 7/24/2013 to 5/24/2014														
HAMS FY 2013	*CUMULATIVE SPENT TO DATE*	% of Total FUNDS Expended	MO 1 - AUG	MO 2 - SEP	MO 3 - OCT	MO 4 - NOV	MO 5 DEC	MO 6 - JAN	MO 7 - FEB	MO 8 - MAR	MO 9 - APR	MO 10 - MAY	MO 11 - JUN	MO 12 - JUL
COST INCURRED	$ 159,480.97	93.78%	$ 99,767.22	$ 38,756.79	$ 20,956.96	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -

			Task 1, 2, 3, 6	Task, 1, 2, 3, 6	Tas, 2, 3, 6	Task, 3, 6	Task 3, 6	Task 3, 4, 6	Task 4, 6	Task 4, 6	Task, 4, 6	TASK 4,6	option task 5	option task 5
HAMS FY 2013	*BUDGET 1*	% of Total BUDGET Expended	MO 1 - AUG	MO 2 - SEP	MO 3 - OCT	MO $ - NOV	MO 5 - DEC	MO 6 - JAN	MO 7 - FEB	MO 8 - MAR	MO 9 - APR	MO 10 - MAY	MO 11 - JUN	MO 12 - JUL
TOTAL BUDGET	$ 170,056.58	100.00%	$ 70,935.88	$ 74,928.89	$ 24,191.81	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
		Projected expenditure % based on 170K budget	41.71%	85.77%	100.00%	100.00%	100.00%	100.00%	100.00%					

HAMS FY 2014	*BUDGET 2*	% of Total BUDGET Expended	MO 1 - AUG	MO 2 - SEP	MO 3 - OCT	MO 4 - NOV	MO 5 - DEC	MO 6 - JAN	MO 7 - FEB	MO 8 - MAR	MO 9 - APR	MO 10 - MAY	MO 11 - JUN	MO 12 - JUL
TOTAL BUDGET	$ 286,040.19	100.00%	$ -	$ -	$ -	$ -	$ 44,196.87	$ 53,243.55	$ 34,325.33	$ 30,929.78	$ 24,021.05	$ 28,253.63	$ 37,392.10	$ 33,677.89
		Projected expenditure % based on $286K	0.00%	0.00%	0.00%	0.00%	15.45%	34.07%	46.07%	56.88%	65.28%	75.15%	88.23%	100.00%

10.0 List of Symbols, Abbreviations and Acronyms

[O2]	Concentration of Oxygen
AMS	Altitude Mountain Sickness
ANS	Autonomic Nervous System
COPD	Chronic Obstructive Pulmonary Disease
DSP	Digital Signal Processing
ECG	Electrocardiogram
EPO	Erythropoietin
FDA	Food and Drug Administration
FTP	File Transfer Protocol
HAMS	Hypoxia Monitoring, Alert and Mitigation System
HRV	Heart Rate Variability
ONR	Office of Naval Research
PaCO2	Alveolar Pressure of Carbon Dioxide
PaO2	Alveolar Pressure of Oxygen
RER	Respiratory Exchange Ratio
ROBD	Reduced Oxygen Breathing Device
SaO2	Arterial Oxygen Saturation Measured via CO-Oximeter
SpO2	Arterial Oxygen Saturation Measured via Pulse-Oximeter
TAILSS	Tactical Aircrew Integrated Life Support System
TUC	Time of Useful Consciousness
USN	United States Navy

11.0 Distribution List

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